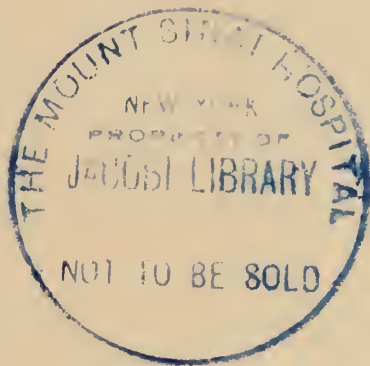






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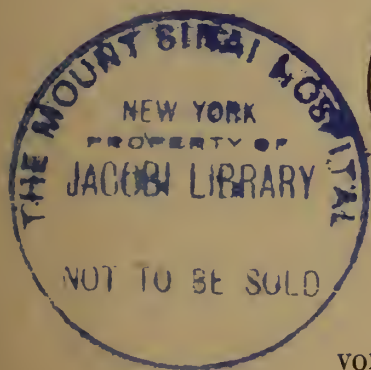
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Manuscripts, abstracts of articles, and correspondence relating to the editorial management should be sent to Dr. Joseph H. Globus, Editor of the Journal of The Mount Sinai Hospital, 1 East 100th Street, New York City.

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INSULIN ALLERGY<sup>1</sup>

## CASE REPORT WITH REVIEW OF THE LITERATURE

JOSEPH HERZSTEIN, M.D., AND HERBERT POLLACK, M.D.

*[From the Medical Service of Dr. George Baehr and the Metabolism Clinic of Dr. Herman Lande]*

It is not uncommon for patients to experience local skin reactions to insulin at the onset of injections. These reactions generally cease with the continued use of the same commercial brand of insulin. When local reactions are excessively annoying, a shift to a different brand of insulin usually obviates the difficulty. This expedient is often ineffective when the insulin injection gives rise to generalized allergic symptoms. A case of this type is reported here.

## CASE REPORT

W. S. (Adm. 402550), a female, presented herself at the Diabetic Clinic of The Mount Sinai Hospital in 1931. She stated that she had had a mild diabetes mellitus for four years. Her father also had diabetes.

A diet of 50 gm. carbohydrate, 60 gm. protein, and 100 gm. fat was ordered. No insulin was required to keep the patient aglycosuric. During the course of the first six weeks' attendance at the clinic, the patient developed pelvic inflammatory disease and required hospitalization. In the hospital the diet was increased to 100 gm. of carbohydrate, 70 gm. of protein, and 120 gm. of fat. Ten units of insulin, twice daily, were required to control the diabetic state. After a brief stay in the hospital she was discharged to the clinic, only to be readmitted in another few weeks. The pelvic inflammation finally subsided, and no further insulin was required. From 1932 to 1936 the patient was observed frequently in the Out-Patient Department. No insulin was necessary during this period to keep the urine free of glucose.

In 1936 there was a marked change in her tolerance. A continuous glycosuria was noted, with transient episodes of mild ketosis. The patient was instructed to take 10 units of insulin twice daily. At the site of each injection she developed an itching area, one inch in diameter, which was red and swollen. After the tenth injection, she developed generalized pruritus associated with erythema and large urticarial wheals over her body. Her eyelids were swollen and her tongue felt thick. The symptoms abated slightly after the injection of adrenalin. A urine analysis at this time showed 4 per cent sugar with some acetone. On account of this abnormal reaction to insulin, she was readmitted to the hospital.

Intradermal sensitivity tests with all available commercial brands of insulin, regardless of animal source (beef, hog, and sheep), all gave positive reactions. Crystalline insulin from two sources (Stearns, Lilly), tested the same way, also resulted in markedly positive reactions. Protamine insulin reacted the same way.

<sup>1</sup> Read at the April 1938 meeting of the American College of Physicians.

The patient showed no positive allergic reactions when tested with beef, hog, or sheep proteins. In other words, she was sensitive to insulin itself, and not to the animal proteins with which insulin is associated. An attempt to desensitize her with the use of histamine phosphate was not successful. In the course of her six weeks in the hospital, the sensitivity to crystalline insulin decreased to the point of producing only local reactions. Ten units of this preparation were required twice daily to control the glycosuria.

It was decided to desensitize the patient to protamine zinc insulin (Lilly). With this brand it was found that a skin test with a dilution of 1:100,000 was negative. The first day she was given 0.5 cc. of this dilution; the second day 1 cc., and the third day 2 cc. The next day 1 cc. of a 1:10,000 dilution was given; then 0.5 cc. of 1:3,000; later, 0.5 cc. of 1:100, and finally 0.5 cc. of 1:10.

With the disappearance of the generalized reactions, she was discharged to the care of the Out-Patient Diabetic Clinic. At first she reported only local reactions, lasting several hours. Two months later, no allergic phenomena of any kind were reported. Her diet is now 120 gm. of carbohydrate, 70 gm. of protein, and 100 gm. of fat, with 24 units of protamine zinc insulin once a day before breakfast.

A final note is of interest. For about a year she had complained of persistent gastro-intestinal symptoms, consisting of pain in the upper right quadrant radiating to the back and right shoulder, not related to meals, but occasionally awakening her at night. Roentgen study failed to reveal any organic basis for her complaints. It was thought that her symptoms might be explained on an allergic basis. She was therefore given all the usual skin tests for foods and other allergens. She did not react to any of them. A gastrointestinal study in January 1938 did reveal a small defect in the posterior duodenal wall. The symptoms disappeared spontaneously.

#### COMMENT

This case presents a non-allergic individual who was given small doses of insulin for a short period without any unusual reaction. Four years later, when she resumed insulin injections, there were local skin reactions. After the tenth injection, there developed a generalized allergic response severe enough to warrant hospitalization. Here she was found sensitive to all insulins, including crystalline insulin, but not to the specific proteins of hog, beef, or sheep. She was successfully desensitized to the brand of insulin which gave her the least reaction and she is now able to use this regularly without discomfort.

#### THE PROTEIN NATURE OF INSULIN

That insulin might cause allergic reactions as do other foreign proteins was recognized from the earliest days of its use. Banting (6), in one of his first papers, says that in the experience of investigators with pancreatic extracts, the chief obstacle to their introduction into clinical use was due to toxic reactions caused by proteins and split protein products. He commented on the rarity of the reactions to the insulin which he and his co-workers introduced. Their explanation was its freedom from protein contamination.

Protein impurities accompanying insulin, as well as preservatives used, have at times been held responsible for untoward reactions. Individual



sensitivity to a single type of animal protein is responsible for the reactions experienced by some patients to one brand of insulin, but not to others. On the other hand there are some patients who are not sensitive to any animal proteins, but who are sensitive to insulin, which by itself can act as a true, specific allergen.

It is generally accepted that the crystalline pure hormone is a protein. Abel (1) described the preparation of pure crystalline insulin, and found that its chemical reactions were characteristic of protein substances. Scott (52) pointed out the similarity of insulins obtained from various sources. He studied crystalline insulin derived from the pancreas of the ox, sheep, hog, and fish. He found the crystals to have a similar microscopic appearance, similar solubilities, similar iso-electric points, and similar carbon, hydrogen, nitrogen, and sulphur content. He found remarkable agreement in the physiological action per unit of solid crystals from the various sources. Jensen (32), in chemical studies of insulin, was able to derive numerous amino-acids from it, and also found that its reactions were characteristic of protein substances. Jensen, Wintersteiner, and Geilung (33) found the crystalline insulin of fish to be the same as beef insulin, with similar physiological activity and similar sulphur content. They regard insulin as a crystalline protein substance.

A uniform sensitivity to insulin in its purest forms and in extremely small doses, suggests a true type of foreign protein allergy. Experimental work in animals and in man indicates that insulin may be a typical allergen. It gives rise in the blood to specific antigenic substances, such as precipitins and other reagins, as demonstrated by passive transfer tests.

Soon after the introduction of insulin, Raymond and Lacroix (48) were able to demonstrate the presence of precipitins in the blood serum of an allergic patient. They were also able to sensitize a guinea-pig with insulin, and then produce anaphylactic shock by injection of the blood serum of an allergic patient,—a form of reverse anaphylaxis.

Tuft (57), in this country, made similar immunological studies in insulin hypersensitiveness. He studied the antibody formation in the blood of an insulin-allergic woman who was sensitive to all insulins, but not to beef or pork proteins alone. Passive transfer tests of the Prausnitz-Küstner type were positive. Tuft also demonstrated the presence of precipitins to insulin in the blood of the patient, but could not detect complement-fixing or anaphylactic antibodies. He found that the precipitins in the blood disappeared early, but that the reagins persisted for three months. He likened the general reaction to that of serum sickness, a form of acquired sensitivity. He suggested that insulin itself is a specific sensitizing substance, not the protein of the animal from which it is derived.

Campbell, Gardiner, and Scott (17) reported a patient who was sensitive to all preparations of insulin, as well as to crystalline insulin, and successfully demonstrated the passive transfer of skin sensitivity to a

normal recipient. Similarly, Karr, Kreidler, Scull, and Petty (36) obtained positive transfer tests from the blood of an insulin-resistant patient who developed extensive local nodules. Her blood serum showed the presence of insulin precipitins. Berger, Hansen, and Eyer (9), Sammis (50), Bryce (15), and Lasch (39) also effected passive transfer in one form or another. Grishaw (27) and Murphy, Beardwood, and Miller (46) were unsuccessful in passive transfer tests.

Cade, Barral, and Roux (16) sensitized guinea-pigs to insulin, and then induced anaphylactic shock with the same substance. They also sensitized dogs to insulin and transmitted the sensitivity to guinea-pigs. In these animals they produced shock with insulin, but not with beef or pancreas protein. They also concluded that insulin was a specific antigenic substance. Barral and Roux (7) sensitized guinea-pigs with saline extracts of beef pancreas and with beef serum, and did not observe anaphylactic reactions in these animals when injected with commercial insulin. They also sensitized guinea-pigs to insulin; these animals did not react to the injection of beef serum or to beef pancreas protein extract. They concluded that insulin was devoid of organ or species sensitivity.

Lewis (43) used the Schulz-Dale uterine muscle technique to study the antigenic properties of insulin. Guinea-pigs were sensitized to insulin, and the uterine muscle strips tested with extracts of beef pancreas, beef serum, and beef insulin. The insulinized animal strips did not react in the presence of beef pancreas or beef serum, but did react to beef insulin. Insulin protein was therefore demonstrated to differ from pancreas protein in its action. The absence of reaction to beef serum, a strongly species-specific antigen, indicated that insulin is not species-specific. Further evidence was obtained by the cross reactions between beef and pork insulins. After sensitizing guinea-pigs with beef or pork insulins, he tested with both homologous and heterologous insulin. There was active reaction in the presence of the heterologous insulin. After desensitizing to the heterologous protein, to which the animals reacted, sensitization to the homologous protein was still demonstrable. He concludes that insulin protein is an active antigen and that it is without species-specificity, since it has no antigenic activity in common with the other proteins derived from the same species, which are strongly species-specific.

#### INCIDENCE AND CASE REPORTS IN THE LITERATURE

The incidence of insulin allergy observed in various centers devoted to the treatment of diabetes mellitus is summarized below.

Joslin (34) in 1922, in one of the earliest reports on insulin therapy, reported the presence of urticarial reactions in 4 patients out of 83. Geyelin (23) and his group who worked with juvenile diabetics, reported that three of them developed serum sickness. One case had generalized urticaria. Wilder (62) and his associates reported 40 cases treated with in-

sulin, 3 of whom manifested allergic reactions. Umber and Rosenberg (58) found 2 cases out of 100 with an urticarial response. One of these they attributed to an idiosyncrasy to tricresol, the preservative. Hallerman (30) treated 541 patients from 1924 to 1930, and saw only 2 hyper-sensitive cases. Greiff (26) commented on Van Noorden's experience, who stated that he had never been obliged to discontinue insulin because of sensitivity.

Allan and Scherer (3), reporting from the Mayo Clinic, found 3.2 per cent allergic among 428 cases treated in 1927, and 13.8 per cent allergic out of 401 cases treated in 1930. Grote (28) met with 5 instances of insulin allergy in 800 cases treated over a two-year period. Davidson (20), in this country, reported only one case occurring in ten years of extensive practice. Murphy, Beardwood, and Miller (46) refer to the fact that local reactions were common, but that there were only 2 cases of 940 with marked general symptoms. Collens, Lerner, and Fialka (19) state that over a three-year period they found 7.3 per cent of 407 cases to be sensitive. Wilmer and Miller (65) studied glucose tolerance in allergic individuals, and state that out of 5,108 allergic cases of all kinds in their records, only two had diabetes or diabetic symptoms. Out of 1,870 diabetic patients of Beardwood, there were only two who were definitely allergic. Bearing on the relationship between allergy and diabetes, Kern (38) reported on a statistical study of 300 diabetics. He found that diabetes and allergy seldom occurred in the same patient at the same time, although in their past medical histories, the diabetics reported a higher incidence of allergic disturbances than did a control group similarly queried. Incidentally, but one case had insulin allergy, and this patient had experienced other allergic manifestations before the diabetes developed.

#### INDIVIDUAL CASE REPORTS

The following is a chronological case review obtained from the literature.

Umber and Rosenberg (58) reported a case which reacted with urticaria to all preparations of insulin, while a second case was sensitive only to insulin Lilly.

Mauriac (45), in 1924, reported on the development of local reactions in a five year old patient in whom insulin had been used for ten months. The local reactions resembled the Arthus phenomenon. Sterile abscess formation resulted from the use of a French brand of insulin. This had to be discontinued and a subcomatose state developed. On shifting to an American brand the acidosis cleared up, and the local reactions did not occur. Mauriac regarded the case as one of sensitivity to an impurity in the insulin.

Sturtevant (56) reported a case with the local development of hard, painful nodules, 1.5 to 2 cm. in diameter, with a surrounding reddened

area 6 to 7 cm. in diameter, lasting seventy-two hours. The condition persisted for six weeks, and gradually disappeared. He considered the reaction to be one of local anaphylaxis, similar to that obtained after the injection of horse serum or diphtheria antitoxin.

Lereboullet, Lelong, and Frossard (42) treated a 4 year old diabetic child, who at first responded well with insulin. She was given measles convalescent serum and diphtheria prophylaxis. After that, each injection of insulin was followed by urticaria and generalized edema. The symptoms abated when the insulin was stopped, but recurred even with a change of brand. When the child developed measles, diabetic coma followed. Insulin was given in a dilution of 1:100 every fifteen minutes in gradually increasing doses from 1 to 10 cc. Each injection was followed by general urticaria and edema. They believed that the intolerance to insulin was a factor in the fatal outcome of the case.

Achard and Bloch (2) described the case of a 30 year old woman who required insulin for nine months and then discontinued its use. An episode of ketotic coma was successfully treated with insulin. She later developed an intolerance, relieved simply by changing the brand of the preparation.

Lawrence (41), in England, early reported a large number of local insulin reactions, modified by changing the brand of insulin.

Raymond and Lacroix (48) report the case of a woman of 64 years who had generalized urticaria and facial edema. Several months later she reacted similarly to a different brand of insulin. Intracutaneous tests were positive.

Roux (49) cites the case of Pehu, that of a two year old diabetic, who experienced local reactions characterized by induration and redness, after the use of several different brands of insulin.

Vedel, Puech, and Reverdy (59) reported on a case of generalized urticaria in a 34 year old woman who started to use insulin and then discontinued it. On its resumption, urticaria developed. Later, the same brand of insulin produced no reaction.

Strauss (54) referred to the fact that 5 per cent of his cases had local reactions to certain insulins, but not to others. Two cases were locally too sensitive to all brands of insulin to continue its use. He refers to a case he saw, one of generalized urticaria who died in diabetic coma. Another had a general exanthem with fever lasting several days.

Walker (60) reported the case of a man of 50 who developed urticaria, general pruritus, and edema of the eyelids. The symptoms diminished by rearranging the diet and insulin dosage.

Bernard (10) reported the case of a severe male diabetic who experienced generalized reactions to two brands of insulin. The reactions were less intense when the patient used diluted insulin. One of his cases developed pseudo-phlegmonous lesions of the thigh which required incision.

Jeanneret (31) reports a man of 22 who took insulin in two series, eight



months apart. In the second course he experienced generalized urticaria. He was gradually desensitized by small doses of insulin starting with 2 units, increased by 2 units at a time.

Engelberg (21) observed a patient with generalized urticaria, swelling of the tongue, and collapse during several courses of insulin therapy. Reactions were later prevented by first giving a fractional dose of 0.1 cc. of the insulin, followed in a short time by the remaining portion of the total dose. Each day the initial dosage was increased by 0.1 cc.

Tuft (57) had a male patient of 62 who had a short series of insulin injections. After omitting insulin he was obliged to resume it, due to an intercurrent illness. There were several injections without any reactions, then an outburst of generalized symptoms. He was found sensitive to the insulins made by Lilly, Mulford, and Stearns, as well as to crystalline insulin. Beef and pork pancreas gave positive skin reactions, while beef and pork protein extract did not.

Bonem (13) reported one case previously treated with insulin. In a second course of insulin the patient had local reactions. After changing the insulin there was edema of the glottis and collapse. Because of continued high blood sugar, insulin was still indicated, and another brand was used, starting with a dosage of 0.1 cc. At first there was a local reaction even to this dose, but later, larger doses, as well as other preparations, were well-tolerated.

Kaufmann (37) had one case in which 4 units gave a marked local reaction, while 64 units of another brand in 2 doses were well-tolerated. A second case with marked local infiltrated reactions to three preparations was desensitized by two small doses of insulin Lilly, 4 to 6 units, given intracutaneously in the course of twenty-four hours. Kaufmann also had a third case, an 8 year old girl, who had generalized urticaria, and facial and eyelid edema. She was given 4 units of insulin Lilly intracutaneously. She later tolerated 24 units a day without reactions.

Campbell, Gardiner and Scott (17) reported the case of a man who was sensitive to beef, hog, sheep, fish, and human insulin, as well as to crystalline insulin.

Williams (63) reported a case of gastro-intestinal allergy. A child treated with pig insulin had such severe gastro-intestinal symptoms that no food could be retained. Intravenous dextrose and salt solution kept the child alive. All symptoms subsided after a shift to beef insulin.

Lasersohn (40) commented on local reactions after insulin, calling attention to the fact that as the injections were continued, the reactions recurred earlier, became less noticeable, and ultimately disappeared.

Hallerman (30) reported an instance of severe local reactions requiring stoppage of the insulin. Another proved sensitive to three brands of insulin; a year later this patient took one of the same brands without adverse effects.

Strooman (55) gave insulin in the treatment of a case of malnutrition. Local reactions developed with the use of one brand of insulin. There were no reactions when he changed to a second brand of insulin until the tenth day, when generalized symptoms did occur.

Karr, Kreidler, Scull and Petty (36) present the case of a woman who for twenty months showed marked sensitivity to insulin. There were painful local reactions lasting a day. Pig, beef, and crystalline insulin gave local reactions. Gradually her insulin requirements rose so that she required 600 to 700 units daily. The patient's serum gave a positive reaction in transfer tests, and showed the presence of precipitins for insulin. For a period of several weeks they sensitized rabbits with the patient's serum. These rabbits were found to develop insulin precipitins in their blood. After desensitizing their patient to ordinary rabbit serum, they injected 5 cc. of serum taken from the rabbits previously injected with the patient's blood. After a week the patient experienced insulin shock symptoms with her usual dose of 650 units. Her requirements for insulin fell to 150 units. Although she still had a diabetic blood sugar curve at the end of the month, insulin could be dispensed with altogether.

Cade, Barral, and Roux (16) reported three cases. One man had urticaria on the eighth day of treatment with insulin; another had a rash and generalized pruritus beginning on the tenth day; while a third patient, a woman, had local nodules with appreciable, localized edema.

Grishaw (27) cited the case of a 38 year old man who had a positive allergic history. At first he developed local tubercles, and later a generalized urticaria with edema. He was skin-sensitive to beef and pork insulins, but not to beef and pork proteins. The attacks were relieved by a change in the insulin preparation. Transfer tests were unsuccessful.

Greiff (26) cited the experience of a colleague with a patient who had two courses of insulin separated by two years. On the eighth day of the second course, he developed a stubborn urticaria. He fared no differently with a change of insulin. He also cited two cases of his own. One was the case of a woman who had taken insulin two years previously. On the tenth day of a second course, she developed generalized urticaria with symptoms of collapse. The use of but two drops of another brand of insulin caused urticaria. Sometime subsequently this patient developed a gall bladder disturbance, and returned in acidosis. Greiff gave her 40 gm. of calcium gluconate by mouth and rectum, together with 1 mg. of atropin, and  $\frac{1}{4}$  gm. of caffeine. After half an hour he gave her 10 units of insulin (Leo). Generalized urticaria set in. The calcium treatment was continued. On the fourth day she received 40 units of insulin without symptoms. A second case had taken insulin a year before. On the fifth day of the second course, urticaria developed. Similar treatment permitted an increase in insulin dosage, and a few days later the

reactions no longer occurred. He believed the sensitivity to be due to non-specific protein substances.

Schill (51) had a patient of 50, who had generalized symptoms, and whom he desensitized over a period of four weeks, starting with an insulin dilution of 1:100,000.

Hajek (29) had a case with large, painful, itching skin lesions, 10 cm. in diameter, which cleared up when a different insulin preparation was used.

Berger, Hansen, and Eyer (9) presented an excellent review of the subject. They had a patient who was skin-sensitive to various brands of insulin, but not to crystalline insulin or to animal serums. Their patient had taken insulin previously with some local reactions. On its resumption, she experienced urticaria, edema of the glottis and tongue, pulmonary edema with bloody expectoration, and a spontaneous abortion. They desensitized their patient over a period of ten days, starting with 1 to 2 units of insulin. They interpreted the sensitivity as being due to some unknown chemical impurity, since the patient failed to show sensitivity to crystalline insulin, or to animal proteins. They were able to effect a positive transfer of the sensitivity.

Allan and Scherer (4) reported an allergic case who was sensitive to all types of insulin. Even the skin testing material caused weakness, paresthesias, and palpitation. She went into acidosis. She was given minute doses of crystalline insulin over a short period, and an efficient dose of insulin could be tolerated on the second day. She was similarly rapidly desensitized to beef insulin. They consider insulin to be not a pure hormone, but a mixture of substances.

Allan and Scherer (3) reported comprehensively on 100 allergic cases from the Mayo Clinic. A mild reaction occurred in 84 cases. This was characterized by a red area, 1-4 cm. in diameter, with possibly a wheal. At times there developed an indurated nodule, 1-3 cm. in diameter, associated with heat or burning which lasted from one to three days. These reactions usually became manifest between the third and fourteenth day of treatment. In 12 instances there were severe local reactions lasting one or more weeks, the areas being as large as 15 cm. in diameter.

In four cases the reactions were general, with skin, circulatory, and gastro-intestinal symptoms. In all cases of insulin allergy intracutaneous tests were positive when made. In 64 cases a change to a different brand of insulin obviated all difficulty. In 8 others desensitization was spontaneous. They report in detail 6 other cases. One woman with a positive personal and family history of allergy, experienced diffuse urticaria, swelling of the face and mucous membranes of the mouth and throat, and prostration. She was partially desensitized to permit an operation. Another case had six injections of insulin. He developed a generalized skin eruption and become completely intolerant to treatment. He was skin-positive to sheep, pig, beef, and crystalline insulin. A third case developed

urticaria on the tenth day. The fourth case, a woman with a positive family history of allergy, but negative personal history, had urticarial reactions. In a fifth case, a woman who developed almost universal urticaria, insulin had to be abandoned after several preparations had been tried. Their sixth case was an allergic woman who had such severe local reactions to all brands of insulin that its use had to be abandoned. She failed to get relief by desensitization. They believe that insulin might contain two kinds of protein, the protein of the hormone itself, and another protein characteristic of the pancreas of the specific species of animal. They also cite a case of Munro who had a male patient of 22, sensitive to all insulins, but least so to crystalline insulin. He was desensitized by adding small doses of beef insulin to crystalline insulin.

Wechsler (61) described the case of an adult female, who when first using insulin experienced local painful infiltrations lasting a few days. On the eighth day after a resumption of insulin, generalized urticaria developed. Later, on shifting to a different brand of insulin and starting with 2 units, no reactions occurred. He believed the reactions were due to tricresol and chlorethane used as preservatives. This patient had earlier experienced an extensive dermatitis due to a preparation containing camphor.

Williams (64) reported another instance of gastro-intestinal allergy. A woman of 52 had been taking insulin for six years. For a period of nine months she complained daily of gastro-intestinal symptoms, consisting of cramps and frequent bowel movements. X-ray studies were negative and surgical intervention was contemplated. Inadvertently she was given beef insulin. Her symptoms cleared up. Skin tests were positive to pork insulin, but not to beef insulin.

Bryce (15) had a woman patient who was sensitive to five brands of insulin, all of which gave rise to generalized urticaria. When given an intradermal test with 0.05 cc., she had a generalized anaphylactic response, relieved by adrenalin. She was sensitive to one-millionth of a unit intradermally. Tests with animal proteins alone, or with diluting fluid or insulin preservatives did not produce typical wheals. She was desensitized, starting with one twenty-thousandth of a unit. Ultimately she took 20 units a day without discomfort. Passive transfer tests of this patient's allergy were demonstrated on two recipients.

Allan and Scherer (5), in writing on the relation between insulin resistance and allergy, report the case of a woman in coma who was allergic to various brands of insulin. She responded but slightly to 500 units of insulin given over a period of twelve hours. She had generalized blebs. When given 150 units of crystalline insulin intravenously the ketosis was overcome, but death due to coronary infarction occurred.

Foerster (22) reported a patient who took insulin with benefit for a time and then discontinued its use. In the second week after its resumption



the insulin proved ineffective, and marked glycosuria as well as acetonuria developed. Generalized urticaria occurred. Insulin in large doses failed to bring about the anticipated effect and was discontinued. Foerster believed that insulin anaphylaxis interfered in some way with the action of the insulin hormone.

Glassberg, Somogyi, and Taussig (25) reported a case of sensitization to insulin in a somewhat unusual form. They treated a diabetic woman who became markedly refractory to insulin. Five weeks after starting insulin, she developed large areas of induration at the site of injection which reached 10 cm. in diameter in twelve to fourteen hours. The area was hot, angry and tender for twelve hours and then faded. An identical response occurred to several brands of insulin. There were no other associated allergic incidents. During the period of these reactions she required huge doses of insulin, the average daily dose being 317 units. She continued the use of insulin, and gradually become desensitized. The local reactions disappeared.

Grote (28) had a case of a generalized reaction with an eosinophilia of 20 per cent. His patient had an increasing tolerance to insulin, and could take three injections totalling 52 units, which rendered him sugar-free. The blood sugar was 210 mg. After a latent period, there was a sudden urticarial attack, and with the customary dose of insulin he developed marked glycosuria, ketonuria, and a rise in blood sugar to 400 mg. More insulin was required for adequate control. He suggests desensitization where a change in the preparation proves ineffective.

Davidson (20) recorded the case of a woman of 62 who resumed insulin four years after an original course. On the fifteenth day she developed urticaria. She was sensitive to crystalline insulin, as well as to the preparations of Squibb, Lilly, and Mulford, while all food tests were negative. Her symptoms disappeared when insulin was discontinued. Her sensitivity gradually subsided as gauged by the local reactions. A few desensitizing doses of insulin were administered. Later she was able to take insulin at will.

Murphy, Beardwood, and Miller (46) presented 2 cases. A woman, who had a few doses of insulin previously, developed generalized urticaria on the fourteenth injection. Intradermally she reacted to all insulins, to beef protein but not to pork protein alone. A second case was an asthmatic woman who experienced marked dyspnea while receiving small doses of insulin. She was relieved by a change to beef insulin. Her reactions appeared on the fourth day of a second course of insulin injections.

Collens, Lerner, and Fialka (19) found that of 30 reacting cases, 27 showed local reactions beginning seven to fifteen days after treatment. Five cases showed reactions to all types of insulin, while in 25, only a change in the preparation of the insulin was required. They desensitized 2 patients over a period of three months starting with 0.0001 units. The

desensitization lasted only a month, however, and the insulin had to be stopped. They also report the case of a 58 year old man who developed severe local reactions twelve days after beginning insulin therapy. Intradermal tests were positive to all insulins, so that he had to be treated by diet alone. He was desensitized with histamine phosphate. Thirteen doses were given, the last four consisting of 1.0 mg. He was then returned to 15 units of insulin a day for six months without experiencing any reactions. They point to the fact that it takes from eight to ten days for the sensitivity to develop, as in serum sickness.

Bayer's (8) case, a woman of 48, took small doses of insulin for a time, then discontinued it. After resuming insulin, she was found sensitive to two brands, one causing a generalized rash, itching, diarrhea, abdominal cramps, and a sense of choking. She was also found sensitive to three other brands of commercial insulin. She was desensitized to Lilly insulin, starting with one one-hundredth of a unit, later diminished to a thousandth of a unit, given at numerous intervals during the course of one day. This proved effective at first; later, however, when fresh bottles of insulin were started, scattered wheals did occur.

Blaisdell (11) reported local reactions in several diabetics, the reactions spontaneously disappearing on continued use of insulin, or on changing the brand. He reported the case of a 58 year old woman who, one hour after the first injection of insulin, developed a local blotch with itching, and later, generalized itching. Her skin had a brawny edema, her voice was husky and she became dyspneic. The symptoms were relieved by adrenalin. When a different brand of insulin was used, there were no general reactions. Local reactions did occur, but these disappeared after two months.

Sammis (50) reports an allergic child who was given 10 units of insulin Lilly to induce a gain in weight. She promptly developed generalized urticaria. She was skin-sensitive to the various insulins.

Lasch (39) reported a case of urticaria and general anaphylactic response to insulin. Positive reactions were obtained with various brands of insulin. He believed that accompanying impurities in the nature of albumoses and peptones were responsible for the reactions.

Bose (14), reporting in the Indian Medical Gazette, described the occurrence of a severe reaction in an elderly physician. He took insulin for eighteen days without any appreciable effect. A year later, 5 units of Mulford's insulin produced embarrassment of the respiratory tract with prostration. There was a futile attempt to desensitize him with small doses of Burroughs-Wellcome crystalline insulin.

Gilberto and Benavides (24) treated a case of anorexia with arsenic and insulin. After the fourth injection generalized urticaria resulted, attributed to the insulin.

Among 100 cases of malnutrition treated with insulin, Blotner (12)

reported 31 per cent as having local skin reactions. These occurred seven to ten days after the beginning of the insulin treatment, and disappeared after several weeks. Three cases experienced a mild urticaria. In one case who was unusually sensitive to a number of proteins, the insulin had to be stopped. One case took insulin some five years previously for three months without sensitivity. Two weeks after resuming insulin, generalized giant urticaria developed one-half hour after the injection.

Stotter (53) recently reported from Umber's clinic in Berlin an unusually hypersensitive case. It was the only one of its kind met with among 8,000 diabetics. The patient was an asthmatic, known to be sensitive to peptone dust. When his diabetes called for the use of insulin, a preliminary patch test with highly purified insulin in a dilution of 1:10 gave a local reaction, while dilutions of 1:100 and 1:1,000 gave no reactions. Following an intracutaneous injection of 0.1 cc. of a dilution of 1:1,000,000 he developed generalized allergic symptoms. He was ultimately desensitized by starting with 0.1 cc. of a dilution of insulin 1:10<sup>7</sup>. Ultimately he was able to take 12 units twice a day. For the usual hypersensitive case Umber recommends the injection of 4 units of insulin twenty minutes before the regular dose.

Finally, Joslin (35) and his co-workers refer to the presence of local skin reactions in users of protamine (zinc) insulin. These are attributed to the fish proteins which are added to such proteins as exist in unmodified insulin. The areas of swelling, redness, and itching which may occur generally arise a few days after the use of the new insulin. In their experience, the local responses almost invariably disappear.

#### COMMENT ON THE LITERATURE

A fairly common feature of all reported cases is the latent period before the allergic manifestations are observed. The sensitivity usually becomes evident when insulin therapy is resumed by patients who have had it in the past and who have discontinued the injections. One group of cases undoubtedly represents an allergy to the animal from which the insulin is derived. These have in common a sensitivity to a particular brand of insulin derived from one animal, but not to another brand derived from a different source.

The real sensitivity to insulin *per se*, regardless of its commercial source, such as existed in the patient observed in our clinic, presents a serious problem. The danger to the patient from anaphylaxis is as real as the danger from diabetic ketosis. It is interesting to note that in this connection, Campbell and McLeod (18) reported that when their first insulin-treated patient returned to them in acidosis, they desensitized him because of the fear of possibly producing an anaphylactic reaction.

Fortunately, desensitization can generally be carried out successfully. The time element in an acute emergency, however, might be the deciding

factor in saving the patient's life. Some of the reported cases seem to indicate that insulin allergy carries with it an inactivation of the physiological functions of this hormone. The case presented here did not show this association.

The experimental data point to the conclusion that insulin may act as a typical allergen. When one considers the thousands of people who daily take injections of insulin, it is surprising that more cases of anaphylaxis do not occur. It is possible that the purified insulins now being used are identical with human insulin. In this case, one would not expect foreign protein reactions, although Lewis (44) showed that goats could form antibodies to their own casein, as well as to cow casein. However, specific sensitization to insulin can occur, as it did in the case presented.

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## FLUOROSCOPIC DIAGNOSIS OF MYOCARDIAL INFARCTION FOLLOWING CORONARY OCCLUSION\*

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In the experience of the author fluoroscopy has become a practical method of making a diagnosis of myocardial infarction due to coronary occlusion. It enables one actually to see the region involved. In the area of infarction there is apparent an abnormal ventricular movement which may assume two main types: a reversal of pulsation, and an absence or diminution of pulsation.

When reversal of, or "paradoxical," pulsation is present, the involved portion expands (outthrust) during systole while the remainder of the ventricle contracts (inthrust). A wave-like or "see-saw" motion is thus seen during systole along the left ventricular border instead of a normal simultaneous contraction of the entire ventricle.

It has been possible to take a motion picture of the movements seen in fluoroscopy (cineroentgenoscopy). Moreover, confirmation of these observations can now be made by roentgenkymography.

Very little has been written concerning fluoroscopy in myocardial infarction (1) and, to my knowledge, only diminution or absence of pulsation has been described. However, it will be shown that reversal of pulsation is far more significant, and this has been mentioned only in relation to ventricular aneurysm (2, 3, 4), a lesion which was found in only two patients in the series to be reported.

The following is a brief history of a patient in whom fluoroscopic evidence of cardiac infarction was first noted in 1934.

### CASE REPORT

*History.* The patient (A. G.), a housewife, fifty years of age, was seen September 2, 1933 at my office, suffering from an anginal syndrome due to coronary artery disease of two years' duration. This required the frequent administration of nitroglycerin. On September 9, 1933, about 10 p.m., while in bed, the patient developed the classical symptoms and signs of an acute coronary occlusion. The diagnosis was confirmed the next morning by electrocardiogram. The changes indicated a posterior infarction, i.e., a Q-2 T-2, Q-3 T-3 pattern was present (Fig. 1A). Recovery followed a rather stormy course. The patient was seen repeatedly in my office. On October 15, 1934, the results of the fluoroscopic examination were recorded as showing that "the apex of the left ventricle bulged in systole instead of contracting." This abnormal fluoroscopic finding persisted, although the patient had steadily improved.

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\* The Roentgenkymography was carried out in the Department of Roentgenology of The Mount Sinai Hospital.

A roentgenkymogram taken April 5, 1939 (Fig. 2) confirmed this. An electrocardiogram taken at the same time showed also the characteristic pattern of myocardial infarction (Fig. 1B).

*Method.* In order to visualize the details of ventricular contraction, sufficient time should be spent for the eyes to become thoroughly accommodated. The Patterson B type of fluoroscopic screen was found to be a real improvement over the previous types.

The patient is asked to take a deep breath and to hold it. At the end of inspiration the heart is slowed, enabling the examiner to observe the

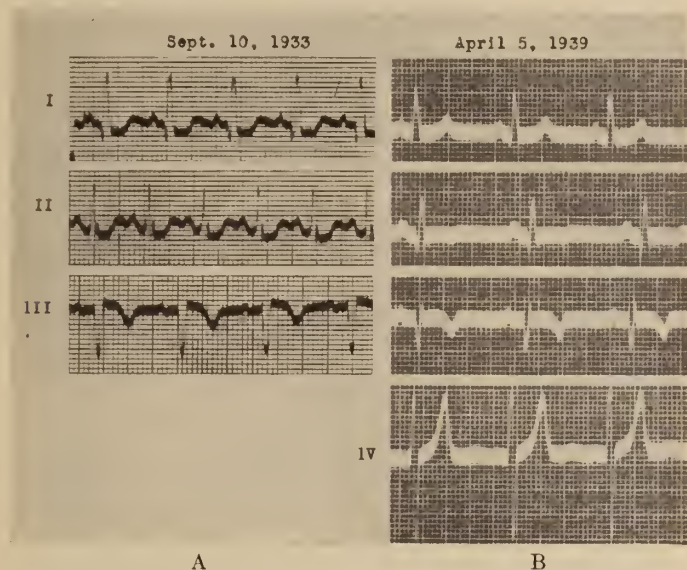


FIG. 1A.: Electrocardiogram taken one day after attack. RS-T segment deviations below and above the isoelectric level characteristic of acute myocardial infarction.

FIG. 1B.: Electrocardiogram, April 5, 1939, shows large Q-2 and Q-3 and inversion of T-2 and T-3, the typical pattern for a previous infarction of the posterior surface of the left ventricle.

ventricular movements in greater detail. Rapid heart action makes it difficult, if not impossible, to study minute movements of the heart. Excessive straining while holding the breath must be avoided, since it increases intrathoracic pressure and, of itself, diminishes ventricular contraction.

It is of paramount importance to time systole and diastole correctly. This is best done by comparing the movements of the aorta (or pulmonary artery) with those of the ventricle. In systole the aorta, as a rule, is readily seen to expand. Normally the ventricle contracts as a whole at this time. After this relationship has been established the opening of the screen, the diaphragm, is diminished and the ventricular border alone is studied.

Formerly the P-A view was relied upon chiefly since details can be seen more clearly in this than in the oblique or lateral positions. However, the latter views have been utilized and recently have been especially studied.

*Material and Results.* The fluoroscopic findings in the last 100 cases of myocardial infarction due to coronary occlusion observed in my office in the past two years form the basis of the study. Four patients were fluoroscoped in the first few weeks of illness, one a few days after the attack.



FIG. 2A.: Teleoroentgenogram, April 5, 1939, reveals a heart of practically normal size and position. It is perhaps slightly enlarged. The aortic knob is prominent.

The period covered in the fluoroscopic examinations varied from a few days to fourteen and a half years after the occlusion. Positive findings were obtainable in any period. It is significant that this was true of the case observed a few days after the attack, as well as of the one seen after fourteen and a half years. Two-thirds of the cases presented the fluoroscopic findings of myocardial infarction, i.e., localized reversal or absence or diminution of contraction.

Reversal or paradoxical contraction was found to be characteristic of



myocardial infarction; it has not been observed in normal hearts. It has been said, however, that diminution in pulsation, and even absence, may also occur when the heart is considerably enlarged and heart failure present.

The exact location of the abnormal pulsation was recorded in 44 cases (Table II). It will be seen that the most common sites were the apex and



FIG. 2B.: Roentgenkymogram in P-A View: Segment 1, normal aortic pulsation; segments 5-6, normal ventricular pulsation, i.e., inthrust during systole, synchronous with outthrust of the aorta; segments 7-10, comprising practically the entire left ventricular border—marked diminution of movement.

supraapical regions. The middle third was not infrequently involved but in only one case was the movement abnormal in the upper portion of the left ventricle. Usually the abnormal pulsation was localized to a small area; however, in 11 cases it extended over the lower half of the ventricle, and in two cases over the lower two-thirds.

In Table III it is seen that positive evidence of myocardial infarction

was observed fluoroscopically in 33, or 62 per cent, of 53 patients with anterior infarction, and in 33, or 70 per cent, of those with posterior infarction. Hence posterior infarction may be recognized in the P-A position as readily as anterior infarction. Six out of seven cases (86 per cent) with infarction of both the anterior and posterior surfaces of the left ventricle were recognized fluoroscopically. Hence it would seem

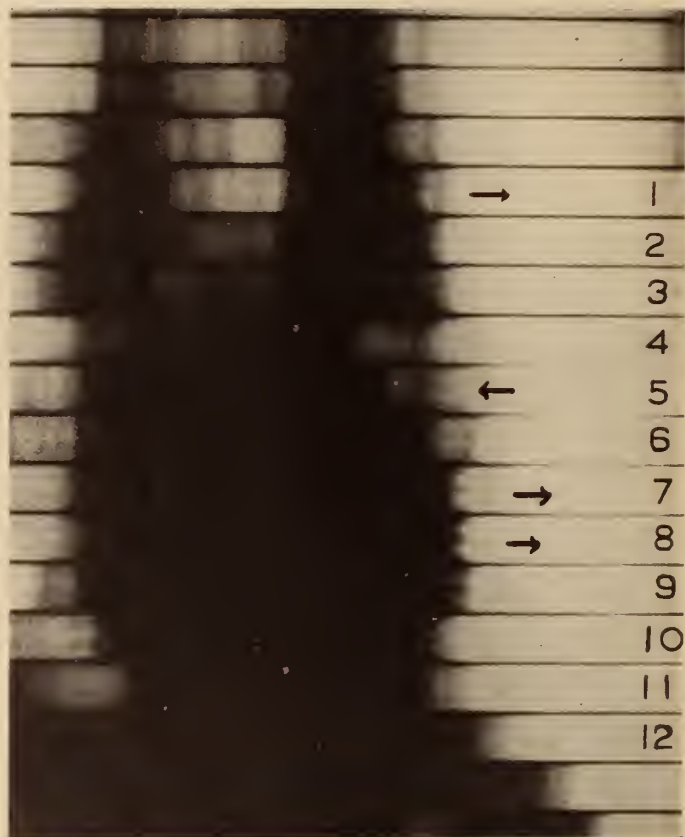


FIG. 2C.: Roentgenkymogram in L-O View: Segment 1, normal pulsation of the descending aorta; segments 5-6, normal pulsation of upper left ventricular border; segments 7-10, comprising lower two-thirds of left ventricular border—complete reversal of pulsation, i.e., there is an outthrust during systole, synchronous with the inthrust of the normal ventricle and outthrust of the aorta.

that the larger the area of infarction, the more apt is evidence of the latter to be present on fluoroscopic examination.

#### DISCUSSION

The recorded observations indicate that myocardial infarction can be diagnosed fluoroscopically in over 60 per cent of cases. This diagnostic method is simple if the physician has had some experience and is moder-

ately careful. Its usefulness is greatest after the acute stage of the attack. It is particularly valuable when the electrocardiogram is normal or not characteristic of infarction. Occasionally the electrocardiographic abnormalities disappear some time after an attack; however, the contractions of the ventricle may remain abnormal, and these can be seen readily on fluoroscopy.

It is noteworthy that posterior infarction, as judged by the electrocardiogram, presents abnormal contractions in the P-A view just as frequently as does anterior infarction. This may be due to the fact that the abnormal contraction affects the muscle bundle in its continuation toward the left

TABLE I  
*Type of contraction observed on fluoroscopy*

CASES EXAMINED	REVERSAL	DIMINISHED OR ABSENT	NEGATIVE
100	39	27	34

TABLE II  
*Location of abnormal pulsation by fluoroscopy*

CASES EXAMINED	APEX	LOWER HALF	MIDDLE THIRD	LOWER TWO-THIRDS	UPPER THIRD
44	22	11	8	2	1

TABLE III  
*Fluoroscopic findings in anterior and posterior infarction as indicated by electrocardiogram*

RESULTS	CASES EXAMINED	ANTERIOR	POSTERIOR	ANTERIOR AND POSTERIOR	NORMAL
Positive.....	67	33	23	6	5
Negative.....	33	20	10	1	2
Total.....	100	53	33	7	7

border of the heart. However, it is my impression, in spite of insufficient data concerning the left oblique and lateral positions, that when posterior infarction is present, the contractions are apt to be more definitely abnormal in these positions than in the P-A. Thus, the pulsation may be diminished in the P-A position, and reversed in the left oblique and lateral. In fact, in two cases in this series the pulsations were abnormal in the latter positions and normal in the P-A. Similarly, when anterior infarction is present, abnormal pulsations are more definite in the P-A position, and may be seen only in this position. However, they are often also evident in the left oblique and lateral positions. Further experience may modify these impressions.

## SUMMARY

1. Fluoroscopic examination reveals abnormal pulsations in two-thirds of patients with myocardial infarction due to coronary artery occlusion. Of 100 cases, the pulsation was normal in 34, reversed or "paradoxical" in 39, absent or diminished in 27. Reversal or "paradoxical" pulsation is characteristic of cardiac infarction.

2. Abnormalities in contraction may be observed a few days after occlusion, as well as years later.

3. The most common sites of abnormal pulsation are the apical and supraapical portions of the left ventricle.

4. In the P-A position, abnormal pulsations are present in both anterior and posterior infarction.

5. If the abnormal contraction is seen only in the left oblique or lateral position, posterior infarction is probably present, and if seen only in the P-A view, the infarction is probably anterior.

6. Greater experience and improvement in fluoroscopic screens will probably raise the percentage of diagnoses of cardiac infarction.

7. Fluoroscopy is a practical and inexpensive method which aids in the diagnosis of cardiac infarction. It may be positive when the electrocardiogram and physical signs are negative.

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# INOCULATION TUBERCULOSIS OF THE SKIN: THE PRIMARY CUTANEOUS COMPLEX

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[From the Surgical Service of Dr. John H. Garlock]

The skin is an extremely rare initial portal of entry for the tubercle bacillus. Based upon post mortem examinations, primary infection by this route has been estimated to occur in only 0.14 per cent of cases of tuberculosis (1). Authentic instances of the primary cutaneous complex discovered clinically are even more infrequent; only sporadic cases are found reported in the literature on this subject. The records of The Mount Sinai Hospital fail to disclose a single recognized example. The rarity of this condition, it is felt, merits the recording of a case of probable primary inoculation tuberculosis of the skin seen recently on the surgical wards of the hospital.

## CASE REPORT

*History* (Adm. 418273): J. T., a male negro child two and one-half years of age, was admitted to the service of Dr. John H. Garlock on December 23, 1937, because of a swelling in the left groin.

His birth and early development were normal. He had previously been entirely well. His mother died of "chronic bronchiectasis and pneumonia," when he was four months of age. Of his paternity nothing could be learned. Two siblings were living and well. The patient had always lived in New York, and almost from his birth, with an aunt who went out to work by the day and left him in care of a neighbor. When his aunt first brought him to the hospital she stated that the child had bruised his left shin two or three weeks previously while playing on the floor at home. This bruise had given him no trouble, and the exact duration of the swelling in the groin was not known.

*Examination:* The child's nutrition and bodily development were good. He did not appear ill but his temperature was slightly elevated. The general examination was negative. Locally there was seen a fluctuant swelling, about 5 cm. in diameter, in the left subinguinal region. The overlying skin was moderately reddened and the lesion was sensitive to palpation. Over the upper portion of the left shin there was a small, encrusted, superficial wound. No other adenopathy was found. Systemic examination revealed no other abnormality. Blood count and smears were normal. Urine analysis and blood Wassermann tests were negative.

*Course:* The patient seemed at first to have an ordinary pyogenic abscess in the groin secondary to an infected abrasion of the leg. The abscess was incised on the afternoon of his admission. Pus was found and evacuated. The appearance of the broken-down lymph nodes found within the abscess cavity gave the first inkling of anything unusual about this case. This tissue looked as if its stroma had become liquefied, leaving behind little but a fibrous framework. There was no gross caseation. The broken-down nodes were removed completely and saved for histolog-



ical examination. The wound was loosely packed with iodoform gauze. As the contents of the abscess aroused the suspicion that the lesion was a possible primary tuberculous complex, a biopsy of the leg wound was then taken. Figures 1 and 2 show the location and late appearance of the leg and groin lesions.

Smears of the pus showed no organisms. Culture yielded no growth. Histological examination of the removed lymph nodes was reported "Tuberculosis; tubercle bacilli found" (S-61378 (Figure 3)). The tissue excised from the leg wound was also found to contain tubercles and tubercle bacilli (S-61433 (Figure 4)).

In order to establish the diagnosis of primary tuberculous complex, the patient was now more thoroughly studied in conjunction with the Pediatric Service. The von Pirquet test (which was not done until the second week after the patient's admission) was strongly positive. Otherwise all examinations were negative. The



FIG. 1



FIG. 2

FIGS. 1 AND 2. The location and the late appearance of the leg and groin lesions

lungs were clear clinically. The first X-ray examinations, performed on January 6, 1938, when the patient had a mild upper respiratory infection, showed slightly increased pulmonary markings on the right side. The next X-ray films of the chest taken on January 25, after the child's "cold" had subsided, showed the lung fields completely clear, and on re-examination by X-ray on February 7, 1938, the chest was negative again. It was the opinion of the X-ray department that all three studies of the chest had failed to show any evidence of tuberculosis. Roentgen studies of the entire spine were normal. Flat plates made of the abdomen disclosed no demonstrable calcified lymph nodes. Gastric lavage was done on several occasions. The removed fluid in each instance was free of tubercle bacilli and negative results were obtained on guinea-pig inoculation.

The patient was discharged from the hospital two months after his admission. At that time both the leg and thigh wounds were fully healed. Unfortunately he was removed to one of the Southern states and attempts to get him back for follow-up examination have so far been unsuccessful.

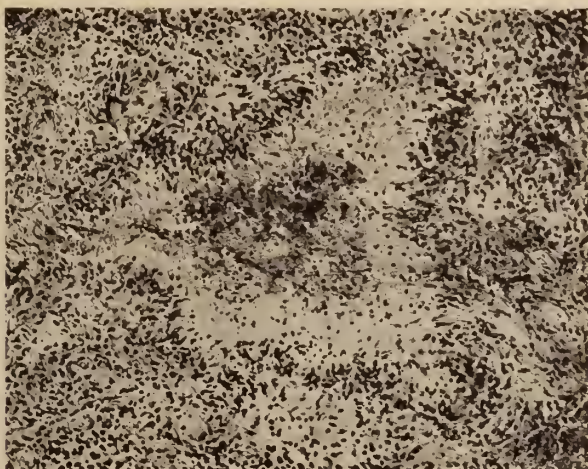


FIG. 3. Tissue from the removed lymph nodes

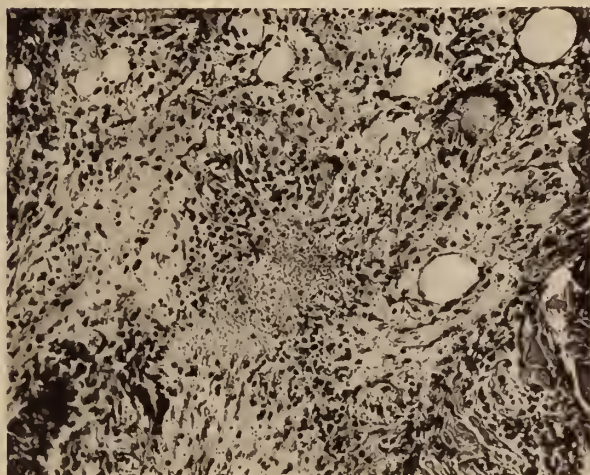


FIG. 4. Tissue from the leg wound

#### COMMENT

Whenever tubercle bacilli, of sufficient virulence and in adequate concentration, gain access to the body of a susceptible individual, who has not previously harbored these organisms, a characteristic train of pathological changes takes place. There first develops, at the site of inocu-

lation, a local lesion followed shortly afterwards by lymphangitis and inflammation of the neighboring lymph nodes. The initial lesion, and the regional lymphadenitis make up the so-called "primary tuberculous complex" (2, 3). This development characterizes a first infection by the tubercle bacillus, as distinct from a reinfection, and is a constant one regardless of the portal of entry of the infection.

The primary lesion is often an insignificant one, innocent in appearance, which usually heals after a relatively brief period. The dominant feature of the primary complex is the adenitis which is acute in onset and goes on as a rule to caseation and suppuration. Often the initial lesion has healed before the adenitis appears and the only evidence of its existence is a healed scar with the associated adenitis.

Tubercle bacilli may enter the body by way of the respiratory or alimentary tracts or through the skin. Of these avenues of infection the former is by far the most frequent and the last of relatively rare occurrence. In any event if the organisms become implanted in a host who does not already harbor a latent focus of tuberculosis, and if they find suitable soil for growth, the typical primary complex results. In cases of primary infection of the upper respiratory passages or the lungs the only demonstrable lesion may be enlargement of the tracheo-bronchial lymph nodes. Similarly when the first infection occurs by way of the gastro-intestinal tract, mesenteric adenopathy may be the only resulting lesion. It is only in the infrequent initial cutaneous invasion that the primary tuberculous complex can be seen in its entirety, and its true nature is usually not suspected before the appearance of suppurative adenitis. The primary complex is not peculiar to external tuberculosis but only in this variety of infection is it characteristically demonstrable.

One of the earliest recognized forms of accidental primary inoculation tuberculosis is that resulting from ritual circumcision (4, 5, 6). The majority of the reported cases of primary accidental inoculation became infected in this manner. Next in frequency have been instances of tuberculous implantation following traumatic wounds of the extremities. Infections in assorted accidental types of wounds have been described following puncture of ear-lobes for earrings, small-pox vaccination, tooth extractions and after kissing and bites, (7, 8, 9, 10, 11, 12, 13, 14). Czerny reported two instances of primary infection arising out of homologous skin transplants (15).

Recorded cases of the primary cutaneous complex are exceedingly rare in this country; most of the published reports are in foreign language journals. The most comprehensive American contributions on the subject are by Michelson (16) and by Stokes (17). Recently case reports have been added by Kereszturi and Siegel (18) and Fidler (19).

Primary tuberculosis of the skin cannot with certainty be differentiated morphologically from an exogenous re-infection. In order to establish



a true instance of primary cutaneous tuberculous complex, certain specific criteria must be met. The etiology of the lesions must first be proved histologically and, if possible, bacteriologically. It is next essential to show that the infection is a primary one—that the individual is entirely free of any healed or latent focus of tuberculosis. Systemic examination, roentgenological, as well as clinical and laboratory tests, must be entirely negative for any such possible focus. Definite proof of the primary nature of the lesion then demands that the tuberculin reaction should be negative at the onset of the infection, later becoming positive. In actual practice the last criterion can almost never be met since the reaction to tuberculin may become positive within a week after the accidental inoculation. The test is rarely done early enough to be found negative. Furthermore, even the tuberculin test cannot be regarded as infallible; it has been found negative in cases of frank tuberculosis with positive sputum (20).

In the case here recorded, as in almost all the reported cases, only presumptive evidence of the primary nature of the infection can be offered. The age of this child, two and one-half years, is an important point. The younger the patient, the more likely is the infection to be an initial one. The sequence of events in this child's history, trauma to an extremity with a small local indolent wound, followed in a few weeks by suppuration in the draining lymph nodes with the adenitis overshadowing the initial lesion, parallels the usual story in these cases. The recovery of acid-fast bacilli, together with tubercles in both the leg and groin lesions, while no evidence of tuberculosis could be demonstrated elsewhere in the body, serves to bear out the contention of the existence in this patient of a primary cutaneous complex of tuberculosis.

*Prognosis.* The ultimate result of primary cutaneous tuberculosis seems to be indeterminate. Except in very young infants, where rapid generalized dissemination of the infection is most often seen, the external complex as a rule has a brief existence. However, instances of late reactivation in old healed primary foci have been described. Complete removal of the involved lymph nodes is advised. Excision of the initial wound is not indicated and may not be safe. Whether the healed lesion serves further by protecting the individual against reinfection, or rather makes him more susceptible to systemic manifestations of the disease, remains as yet an unsettled problem (2, 20, 21). Its fate depends probably upon the degree of individual resistance which cannot be foreseen in any specific case.

#### CONCLUSION

This publication intends merely to record an instance of probable primary tuberculosis of the skin arising through direct inoculation in a minor traumatic wound. It is hoped that this report may serve to facilitate the recognition of other similar cases. It seems not unlikely that

occasional examples of this entity have been unrecognized and considered instances of ordinary pyogenic infection. Biopsy is indicated in accidental wounds occurring on the extremities of children where there exists a regional suppurative adenitis which is disproportionate to the initial lesion.

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## PRESACRAL DERMOID CYST

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The sacro-coccygeal region is the site of important and complex embryologic activity. It is, therefore, not surprising that it is one of the most common locations in the body for a wide variety of anomalous tumors. In this region, the caudal end of the primitive streak develops and subsequently undergoes involution; the neurenteric canal is formed and later disappears; the proctodeum invaginates and joins with the hind gut; the post-anal gut atrophies and the sacrum and coccyx develop. A short distance away complicated changes occur in connection with the evolution of the genito-urinary tract. All three types of embryonal tissue participate in these changes. It is apparent that any small developmental error or the failure of a part to completely atrophy may leave a nidus capable of further growth. These growths are so varied that they have been appropriately called by Rindfleisch (1) an "histological potpourri." Hundling (2) states that the following have been found: teratoma, dermoid cysts, gliomata, giant cell tumors, sarcomata, carcinomata, fibromata, chondromata, osteomata, lipomata, chordomata, angiomata, epitheliomata, endotheliomata, mixed tumors, fetal inclusions, and abnormally persisting caudal appendages. These tumors have been popularly known as "Middledorpf" tumors, but it is correctly suggested by Whittaker and Pemberton (3) that this term should be applied only to those teratomatous tumors arising from the post-anal gut, as described originally by Middledorpf.

All presacral tumors are rare and dermoid cysts are, naturally, even more so. Colbet (4) found presacral tumors occurring once in 34,582 births. Hundling reported nineteen cases of tumor ventral to the sacrum, four of which were dermoid cysts. Whittaker and Pemberton state that tumors ventral to the sacrum occurred once in 40,000 registrations at the Mayo Clinic. Inasmuch as they report twenty-two cases of presacral tumor, nine of which were dermoid cysts, it is apparent that presacral dermoids occurred approximately once in every 97,000 registrations.

Presacral dermoid cysts may occur at any age, having been found in infants, as well as in the aged. These tumors apparently occur only in females. No instance of a presacral dermoid in a male has been found in the literature. This curious sex predilection has not been explained.

There are no constant or pathognomonic symptoms. The most frequent

symptom is low backache or dull aching pain over the lower sacrum and coccyx. Sometimes the patient is aware of a swelling in the region of the coccyx. The reports indicate that these tumefactions may either be incised, or rupture spontaneously, with resultant chronic discharging sinuses. Multiple discharging sinuses in the ano-coccygeal region are not unusual in patients with presacral dermoid cysts (5). An unusual symptom reported by a number of writers—Port (6), Bland-Sutton (7), Lockhart-Mummery (8 and 9), Fried and Stone (10)—has been the protrusion of hair from the anus. In some patients, the hair appeared only on straining during defecation. In others, however, the growth of hair was so abundant that it required frequent cutting. This bizarre symptom naturally occurred some time after rupture of the cyst into the rectum. Other symptoms that have been reported were constipation, rectal pressure, pelvic discomfort after defecation, and partial rectal and urinary incontinence.

The most common finding on physical examination is a rectal mass felt above the anal canal, ventral to the sacrum. This mass is invariably covered with apparently normal rectal mucous membrane, and may feel smooth, firm, or cystic. The size may vary from that of an egg to that of a small grapefruit. If the cyst has ruptured through the peri-anal tissues, lateral to the sacrum and coccyx, discharging sinuses may be found. Proctoscopic examination usually reveals a normal-appearing rectal mucosa unless rupture of the cyst into the rectum has previously occurred. Roentgenological examination may, in some instances, reveal the presence of teeth in the pelvic mass.

The treatment of this condition is surgical. Attempts have been made in the past to excise these cysts through the rectum, or, when the growths were large and presented anteriorly, through an abdominal incision. These approaches presented great technical difficulties, and the consequences were often serious. The usual and correct approach is through a posterior incision, with or without excision of part of the sacrum and the coccyx. The cyst may thus be excised with very little danger of untoward complications.

#### CASE REPORT

*History* (I. W., Adm. 417954). A 47 year old, white, married female, consulted her family physician because of headaches and dizziness. She had always been constipated and, on rare occasions, had slight rectal bleeding upon defecation. The history was otherwise entirely negative. Her physician, in performing a general physical examination, discovered a rectal mass and referred her to the rectal clinic on December 8, 1937.

*Proctological examination. Inspection:* The anus was normal except for the presence of a few small skin tags. The sacral and coccygeal regions appeared normal. *Palpation:* The anal canal was normal. A smooth, firm, oval-shaped mass, about the size of a small grapefruit was felt on the posterior rectal wall. It began



about two inches above the mucocutaneous junction and extended upward beyond the tip of the examining finger. The mass was fixed to the posterior rectal wall and the mucous membrane overlying it was unbroken and freely movable. *Anoscopy*: Several small internal hemorrhoids were present. The mucous membrane overlying the mass appeared entirely normal. *Sigmoidoscopy*: The instrument was passed without difficulty. The mucosa appeared normal throughout.

General physical examination was essentially negative.

*Laboratory Data.* The blood Wassermann test was negative. The urine was negative. X-ray examination of the pelvis revealed no abnormality of the bones. There was no definite evidence of a soft tissue mass in the pelvis, nor were any calcified shadows seen.

*Course.* A diagnosis of presacral cyst was made and the patient was referred to the hospital. On December 20, 1937, the patient was operated upon, under general anesthesia, by Dr. John H. Garlock. A medial incision was made starting from the lower end of the sacrum and continuing to a point about one inch below the coccyx. The coccyx and last segment of the sacrum were removed, bringing into view a round, cystic tumor. The mass was closely adherent to the posterior rectal wall and was separated from the rectum only by mucous membrane. To facilitate its removal, the cyst was opened and its contents evacuated. The entire sac wall was then easily removed by sharp dissection. The wound was thoroughly irrigated. The fascia across the posterior aspect of the rectum was sutured with interrupted chromic catgut and the dead space was packed. The skin was approximated with interrupted silkworm-gut sutures.

Pathological examination of the specimen confirmed the operative diagnosis of dermoid cyst.

The patient made an uneventful recovery and was discharged on the fourteenth postoperative day. She was last seen in the Rectal Clinic on April 11, 1938. The wound was completely healed and digital examination revealed a normal rectal ampulla.

#### SUMMARY

A dermoid cyst, ventral to the sacrum, was removed through the posterior route. This cyst occurred in a woman of forty-seven and had caused no symptoms. These tumors are rare and apparently occur only in females. As far as can be determined by a search of available records, this is the first case of a presacral dermoid cyst encountered in The Mount Sinai Hospital.

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# LATENT CARCINOMA OF THE MAIN BRONCHUS OBSCURED BY MASSIVE PLEURAL EFFUSION

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Carcinoma of the lung is often obscured clinically, as well as radiographically, by a massive pleural effusion, serous or bloody, which covers the lung from apex to base. This effusion may be the only clinical manifestation of the neoplasm. There may be no cough, and the indication for bronchoscopy may, therefore, not be apparent for a long time. The following case is reported because it illustrates the value of bronchoscopy in determining the underlying cause of a massive pleural effusion.

## CASE REPORT

*History* (T. H., Adm. 416014). A woman, 36 years of age, was admitted to the medical service of Dr. George Baehr on January 14, 1937, with a history of left-sided chest pain, dyspnea, and fever for a period of three weeks. There had been no cough until three days before admission when she developed a slight non-productive cough. Twenty-five years previously there had been an episode of cough, fever, and bloody sputum, diagnosed as tuberculosis. After five months of rest treatment she became symptom-free.

*Examination.* There were signs in the left chest typical of a large effusion. The heart and trachea were displaced to the right. Moderate clubbing of the fingers and toes was noted. Roentgenographic examination of the chest (Fig. 1) showed a massive pleural effusion filling the entire left chest and displacing the mediastinum to the right. Because of the comparative youth of the individual, the recent onset, the presence of fever, and the history of tuberculosis during adolescence, a tuberculous pleuritis was suspected. The Pirquet test was positive but four examinations of the sputum failed to show the presence of tubercle bacilli. The sedimentation time of the blood was 28 minutes (Linzenmeyer technique).

*Laboratory Data.* The left chest was aspirated and 900 cc. of clear, straw-colored fluid were removed. The fluid had a specific gravity of 1022, and contained 12,000 leukocytes per cubic millimeter, 95 per cent of which were lymphocytes and 5 per cent polymorphonuclear leukocytes. Tubercle bacilli were not found in the fluid. A guinea-pig was inoculated with the pleural fluid, but was reported negative after the patient had been discharged. The pleural fluid was not examined for the presence of tumor cells, and the patient was not bronchoscoped.

*Course.* After a stay of two weeks in the hospital, during which her temperature remained normal, the patient was discharged with the diagnosis of serous pleurisy, probably tuberculous.

Subsequently she was admitted to two other institutions. At each, the same diagnostic investigations were repeated. At the first, she was also considered tuberculous and was given pneumothorax treatment. At the second, the pleura was inspected through the thoracoscope, but in neither institution was the patient bronchoscoped.

Between February and October 1937, her chest was tapped about once a week and the pleural fluid gradually became bloody. On October 29, 1937, nine and a half months after the first admission, she was readmitted to this hospital. She had not lost any weight, but the cough had increased in intensity and she had a temperature of 101°F. At this time, after the persistence of the effusion for almost a year, the possibility of the presence of a carcinoma was first seriously considered. The roentgen film now showed a large collection of fluid and air in the left chest, shrinkage of the left lung, and marked displacement of the mediastinum to the right. Several hundred cubic centimeters of bloody fluid were removed on two occasions, but careful search failed to reveal any tumor cells in the exudate. The indication for bron-



FIG. 1. X-ray picture of the chest, taken on January 15, 1937. A massive pleural effusion fills the entire left chest and displaces the heart and mediastinum to the right.

choscopy became apparent when one day the patient expectorated a moderate amount of bright red blood. Bronchoscopy was performed by Dr. Rudolph Kramer. A hard, firm mass was found arising from the lateral wall of the left main bronchus, below the upper lobe orifice. Biopsy showed adenocarcinoma.

The patient died at home on January 7, 1938. A post mortem examination was not done.

#### COMMENT

It is well-known that the neoplasms arising in the substance of the lung (parenchymal type) and those arising from the small bronchi (peripheral

type) often do not give rise to cough. Even if the neoplasm is situated in one of the main bronchi, as in the case reported here, the patient may not cough for a long time. The patient's symptoms may be due to metastases, and if the latter are in the pleura, the only clinical manifestations may be those of a pleural effusion. Although the most common cause of a serous pleural exudate in persons below middle age is tuberculosis, the finding of clubbing of the fingers, in association with the effusion, should lead one to suspect the presence of an underlying neoplasm. If, as in this case, the effusion fills the entire hemithorax and fails to show evidence of absorption for a considerable period of time, the suspicion of a neoplasm should become even stronger. Failure to find tumor cells in the pleural fluid does not disprove its carcinomatous origin. Since neoplasms in the main bronchi are easily accessible for bronchoscopic biopsy, the indication for this procedure in a case such as the one reported here is evident.

## CYLINDROMA (MIXED TUMOR) OF THE PAROTID REGION WITH VISCERAL METASTASIS

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[From the Department of Laboratories]

The following case is an instance of the rather rare form of cylindroma of the parotid region with visceral metastases; only six similar cases are recorded in the literature.

### CASE REPORT

*History* (Adm. 340759). A 33 year old single woman was admitted to the medical service of Dr. G. Baehr in December, 1932. This was her third admission to a hospital for the removal of a tumor of the parotid region. At the age of 19, that is, fourteen years before death, she noted a pea-sized nodule below the angle of her right jaw. The nodule produced no symptoms and did not increase in size until seven years after it was first noted. At this time, in 1925, it suddenly grew to the size of a plum and was removed surgically. In 1927 she was again hospitalized because of a recurrence of the tumor mass. At a second operation the tumor was again removed and radium treatment begun. A severe pain in her face had begun a short time after the first operative removal, and she likewise sustained a facial palsy. Histologic sections of both tumors removed showed "cylindroma".

Between 1927 and 1932, the patient suffered almost constantly from symptoms of a trigeminal neuralgia. Her pain involved all regions of her face on the right side, i.e., her upper lip, lower jaw, and the right side of her nose, right cheek, and forehead. She had sensations of swelling and numbness occasionally in the right lower jaw region and pain in the upper teeth. The patient was likewise unable to chew, move her lips, or wink the right eye.

*Examination.* The patient was a 33 year old haggard, emaciated woman who looked much older than her stated age.

There was a marked deformity of the right side of her face. The preauricular region on the right side was swollen, hard, and very sensitive. The submandibular region was depressed, hard, and filled with scar tissue. The skin over the right side of the face showed evidence of a radium burn. There was a complete right peripheral facial palsy. There was diminished sensation over the distribution of the fifth nerve, i.e., the nose, face, and tongue; weakness of the motor fifth; and eighth nerve deafness of the right ear. At this time she also showed a moderate bilateral papilledema.

*Course.* A diagnosis of a progressive expanding intracranial lesion was made. Although it was realized that nothing radical could be done, it was nevertheless felt that relief of the patient's pain might be accomplished by section of the right sensory root of the trigeminal. This was done by Dr. Ira Cohen. As the dura was exposed over the temporal lobe it was found to be obscured and displaced by tumor tissue. All landmarks were obliterated. The fossa for the Gasserian ganglion was filled with tumor tissue. The root was cut by blind dissection. The patient was relieved of her pain and discharged.

A specimen removed was reported "cylindroma".

*Second Admission (November 8, 1932).* The patient returned to the hospital because of a hypopion corneal ulcer and a neuroparalytic keratitis. A plastic lid suture was done and she was somewhat relieved.

*Third Admission (December 29, 1932).* Upon this final admission the patient complained of symptoms due to increased intracranial pressure. Her course had been progressively poor. She had lost weight, had had many dizzy spells, fainting spells, and vomiting.

The patient was an emaciated, pale, uncoöperative woman who appeared drowsy. In addition to all the previous findings, a mass was found bulging into the pharynx on the right side filling the tonsillar fossa and projecting into the mouth. She became comatose and died three weeks after admission.

#### NECROPSY FINDINGS

*Local lesion.* There was a globular egg-sized nodular mass overlying the right mandible; it invaded the zygoma and the ramus of the lower jaw and extended directly through the latter to form another ovoid tumor on the inner aspect of the mandible. The mass involved the submaxillary triangle and extended upward along the floor of the mouth beneath the mucous membrane of the pharynx. The pharyngeal mucosa was not invaded but it bulged into the oral cavity.



FIG. 1. Recurrent cylindroma of the parotid region. Note that the tumor is nodular, discrete, well-encapsulated; the dura is intact; the petrous portion of the temporal bone is in parts destroyed by pressure changes.

*The Brain.* The right temporal region showed an operative bony defect about one inch in diameter. The calvarium separated easily from the dura and no tumor nodules were seen on the surface of the dura. The right temporal lobe was markedly eroded on its ventral surface by a tumor mass lying in the middle fossa. For the most part the tumor mass appeared to be well separated from the brain substance and easily elevated from it. However, in a few areas, there were adhesions. The tumor measured 8 by 4 by 5 cm., was hard, nodular, and compact. An extension of the main mass, 3 cm. in diameter, was found subtentorially as an extension into the posterior fossa. This portion pressed upon the right lobe of the cerebellum, the lateral margins of the pons and medulla oblongata. Another portion was adherent to the sella turcica which it filled.

The petrous portion of the right temporal bone showed atrophy and extension of the tumor from the neck through the floor of the middle fossa (Fig. 1).

*Lymph Nodes.* There were a number of shotty cervical lymph nodes on the right side. These had lost their original structure and were infiltrated by tumor tissue.

*Lungs.* The parenchyma of both lungs was riddled with sharply circumscribed, hard, yellowish-white tumor nodules varying in size between 5 mm. and 3 cm. (Fig. 2). Viewed with a hand lens the tumor seemed to be made up of cylindroids.



*Liver.* The liver weighed 1650 grams. About one-half of the superior portion of the right lobe was replaced by a sharply circumscribed confluent mass of tumor tissue similar to that seen in the lungs (Fig. 3).

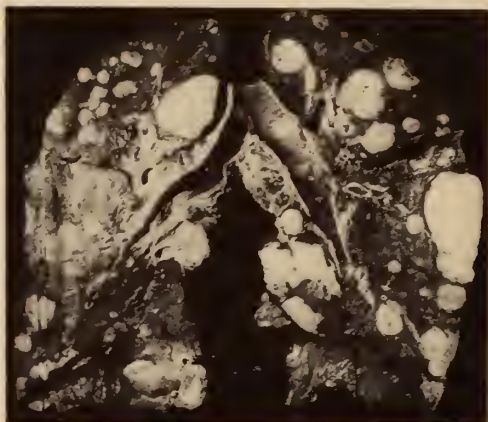


FIG. 2. Metastases of cylindroma to both lungs. Note that the metastatic nodules are likewise discrete, encapsulated, and multiple and have an appearance similar to the local lesion.

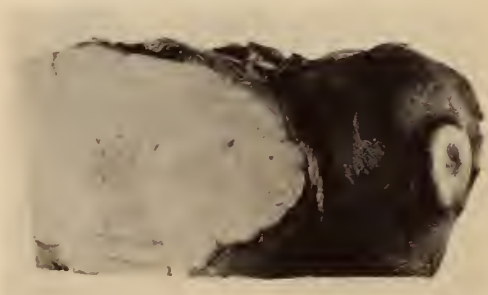


FIG. 3. Metastases of cylindroma to the liver. Note the massive involvement and the appearance similar to the lung metastases.

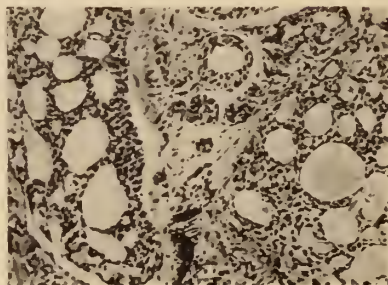


FIG. 4. Microscopic section of the cylindroma of the parotid region. Note the microscopic picture of this lesion. All of the metastatic lesions showed a similar picture.

*Microscopic Examination.* Histologically, the recurrence in the neck and lymph nodes, and all the metastatic tumors presented an identical appearance. The tissue showed branching, interlacing, homogeneous, hyaline, mucoid, cylindrical rows of globules, lined by small cells in single or double rows. These cells resembled basal cells and at first glance a cross section seemed to reveal acinar structure not unlike that of thyroid tissue (Fig. 4).

*Summary of Anatomic Findings.* Recurrent cylindroma of the right parotid gland with invasion of the mandible, zygoma and temporal bone, with extension to the middle and posterior fossae and bulging into the rhinopharynx.

Cylindroma extension to base of skull with compression of cerebral hemisphere, pons, and medulla.

Status after repeated resection of cylindroma of the right parotid region.

Multiple metastatic tumors of both lungs and pleural surface of left diaphragm, liver, and cervical lymph nodes.

#### DISCUSSION

The cylindroma of the parotid region must be classified as a form of mixed tumor. It is clinically encapsulated, freely movable under the skin, and slow in growing. It is non-infiltrating and easily enucleated at operation. The tumor thus behaves like any other mixed tumor. It likewise occurs frequently at the site of other mixed tumors and is prone to recur. Mixed tumors of the parotid frequently contain cylindromatous areas.

The term "mixed tumors of the parotid gland" deserves modification to "mixed tumors of the parotid region," if that is the location in which they are found.

The tumor itself has no other relationship to the parotid or any other salivary gland except for proximity. Mixed tumors and cylindromas are found in other regions of the body such as the soft palate, hard palate, the face, the gums, the neck, the thigh, and the vulva (1). Whenever removed and studied the tumor is found to be distinct in itself, having no gross or histological connection with the glandular structure (Fig. 5). It may grow within the connective tissue septa of the gland but does not invade the glandular structure or appear to arise from glandular tissue.

After reviewing a series of three hundred "mixed tumors of the salivary glands," unquestionably the largest series reported thus far, McFarland (2) states "It seems very difficult to arrive at any satisfactory conclusions with respect to the mixed tumors—their nature and origin are uncertain, their structure various, correlation between structure and clinical behavior contradictory, and the efficacy of any of the methods of combating them doubtful."

This statement is made about mixed tumors with local recurrences. If to that is added the prospect of a benign-appearing tumor producing metastases which in themselves appear benign histologically, then the problem becomes even more distressing. And yet that is the situation

with the cylindroma in the case reported. There are only six other similar authentic cases reported in the literature (3).

The tumor cannot be considered malignant from the start. It took seven years for it to grow from the size of a pea to the size of a plum. The histologic structure alone cannot designate the tumor as a malignant one. And finally, even at the post mortem examination all of the structures that appeared grossly invaded were only displaced or affected by pressure changes. The tumor itself remained well-encapsulated and caused damage by extension to vital centers and not by infiltration. Death in this case was most likely due to an expanding intracranial lesion with pressure on the brain and medulla. Except where there was operative tearing, the tumor was well-encapsulated throughout.

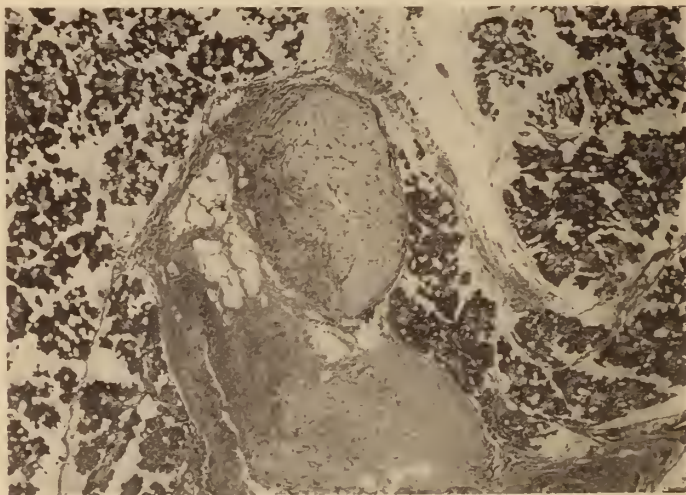


FIG. 5. Invasion of the interlobular septa of the parotid gland by isolated, well-encapsulated mixed tumor nodules. The parotid gland itself is not invaded.

The idea that the tumor metastasized because it was transformed from a benign to a malignant tumor cannot be sustained. There was no such change. The histologic structure of the metastatic tumors is identical with that of the local recurrence. There was no evident so-called malignant metaplasia. There was but one change and that was the rapidity of growth.

It cannot be argued that this tumor was neglected because it was not removed until seven years after it had been discovered. Experience has proved that it is not advisable to remove these tumors when they are very small. Recurrences after removal of smaller tumors are relatively more common than after removal of larger ones. Recurrences among a series of 39 cases observed at The Mount Sinai Hospital have numbered 14, or

30 per cent. Four cases had two recurrences and one had three recurrences. Recurrences take place with both larger and smaller tumors.

The histologic structure of the mixed tumor can not be taken as an index to its malignancy. Cases which appear histologically invasive frequently run a benign course after removal.

Invasion of the capsule likewise cannot be taken as a criterion. There were many more cases with capsular invasion (24 out of 39) than with recurrent tumors (14 out of 39).

Recurrences may be based upon another factor and that is the fact that the tumor, being formed of small nodules, does not always lend itself to complete removal (Fig. 5). (A microscopic focus may be left and this would be sufficient as a nucleus for the next recurrence.)

*Treatment.* Excision of the tumor mass when it reaches a 'ripe stage' is the one recommended. In the region of the parotid it is wisest to operate when the tumor has reached the size of a plum, as injury to the facial nerve is very likely to occur. Radiotherapy has been used and the tumor may be classified as radio-resistant. Radiotherapy neither stops the growth nor does it prevent metastasis. Complete excision apparently is the only radical cure for this tumor, even at the expense of very important surrounding structures.

*Conclusions.* Of the mixed tumor growths the cylindroma is most likely to produce metastases.

Radical removal of the whole tumor, whenever possible, is advised even if vital surrounding structures are destroyed in the operation.

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## Leopold Jaches

December 28, 1873-January 23, 1939

Leopold Jaches was born in 1873, in the Russian Baltic Province of Courland, now Latvia. He came to America in 1892 having already graduated from "Gymnasium." In response to his early inclination he studied Law and was admitted to the New York Bar in 1898. He had become an American citizen the year before. However, shortly thereafter he determined to study Medicine and obtained his doctor's degree in 1903 from the College of Physicians and Surgeons, Columbia University, New York. Upon graduation, he taught Histology at the Cornell University Medical School for some time. Here he became interested in microphotography working with Professor Leaming. This existence and his love for careful and precise technique led him into the then new field of roentgenology and brought him in 1907 to Hamburg to study with Albers-Schönberg, who made a profound impression on him. He realized there, that perfect technique was the fundamental basis of correct interpretation, a principle which he emphasized throughout his life. He remained meticulous to a fault. He developed also a healthy respect for the potential dangers of X-Ray radiation.

On July 1st, 1908, he became Chief of the Roentgen Department of The Mount Sinai Hospital, New York, succeeding the late Dr. Walter Brickner. Concerning the Department, Dr. Jaches once wrote as follows: "From small beginnings this Department developed during the succeeding years into a large diagnostic and therapeutic institute through the aid of the Board of Trustees, and the particular personal interest of the late Mr. Jacob Emsheimer, and the more recently deceased Mr. Ernest Rosenfeld. In this connection, I must not fail to mention the sympathetic cooperation of Dr. Joseph Turner, Director of The Mount Sinai Hospital." At the time of his appointment, the Department was housed in a single room next to the Operating Rooms. Later the present Radiotherapy quarters housed both the diagnostic and therapeutic branches. In 1923, the Diagnostic Service moved into its present location.

Early in 1917, Dr. Jaches was commissioned a Captain in the Medical Corps of the U. S. Army and in July 1917 was ordered for service at the New York School of Military Roentgenology, where he subsequently became an Instructor. The variety and completeness of the instruction which remains collected in an informal volume in the Department, reveal vividly the personality of the one who had so much to do with its execution,



of his careful attention to detail, but withal an amazing comprehension of the entire field.

In 1918, he was promoted to the rank of Major, and was sent to France in charge of a group of X-Ray mechanics and technicians described as Roentgen Unit No. 1. Later he became Assistant to Col. Arthur C. Christie, M.C., who was Senior Consultant in Roentgenology. In early 1919, when Dr. Christie was ordered home, Dr. Jaches was appointed his successor and was promoted to Lt. Colonel. By June 1919, his job was completed and he was ordered home.

From 1919, Dr. Jaches returned to private practice but devoted himself mainly to the development of the Department of Radiology at The Mount Sinai Hospital. Although inherently cautious, his direction was progressive so that the Department was always in the vanguard when new methods were being used. New developments described in the literature and noted by Dr. Jaches while attending National and International meetings were rapidly incorporated into the routine work after careful consideration indicated that they were desirable. For example, this Department was one of the first in this Country in which the equipment was completely electrically shock-proof.

Dr. Jaches threw himself eagerly into any movement which had as its object the betterment of Radiology. In 1908, he was elected to membership in the American Roentgen Ray Society which, in 1930, honored him by electing him its President. In 1923, he joined the Radiological Society of North America and in 1933 became a Fellow of the American College of Radiology. In 1936, the American Roentgen Ray Society appointed him to the American Board of Radiology. In July 1936, he was appointed Clinical Professor of Radiology at Columbia University. He was a charter member of the New York Roentgen Society and a Fellow of the New York Academy of Medicine. He was the Consultant Roentgenologist to the Montefiore and Norwalk Hospitals.

The dynamics of this modest man cannot be expressed by the narration of events. Nor does the listing of his publications and honors give sufficient indication of his service to the Art and Science of Radiology because, so often, he insisted on remaining in the background and letting the others do the writing and presenting. He was one of the first Radiologists in New York to be interested in retrograde pyelography and retrograde cystography. The book on "Clinical Roentgenology of the Chest" by Wessler and Jaches is still a standard text and for many years was the only satisfactory English textbook on this subject. His more recent contributions on pulmonary suppuration, osteolytic bone tumors, the roentgen diagnosis of urinary diseases are too well-known to need special comment.

Internationally known, Dr. Jaches was a pioneer. He was welcomed to the deliberations of those who steer the course of Radiology, often himself

guiding, though always self-effacing. His outstanding characteristic was his honesty and his intolerance of anything which smacked of dishonesty. It is said that he never spoke a mean word. Those who knew him realized that Dr. Jaches was kind, warm-hearted, and generous. To some, he may have appeared indifferent but this was but an attempt to disguise his inherent modesty. As a friend, he was faithful; as a preceptor, he was inspiring; as an associate, he was loved and respected. His work at The Mount Sinai Hospital has been fully appreciated: the Department is his memorial.

MARCY L. SUSSMAN.

## CLINICAL PATHOLOGICAL CONFERENCES

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, January 19, 1938*

Foreign Body (Chicken Bone) Lung Abscess with Empyema  
in an Infant, Three Weeks Old.

*(From the Surgical Service of Dr. Harold Neuhoof)*

*History* (Adm. 412817; P.M. 10473). An eleven week old male infant was brought to the hospital because of cough of eight weeks' duration and fever of two weeks' duration. The child was a normal, full term delivery and weighed eight pounds at birth. The feedings and weight gain were normal and the general condition remained good. However, beginning with its fourth week, the infant commenced to cough, sneeze, and expectorate mucoid material. At the age of nine weeks, the infant's temperature rose and ranged between 101°F. to 103°F. With this an increase in cough and expectoration occurred. One week later the diagnosis of pneumonia was made by the family physician. On the day before admission to this hospital, purulent fluid was aspirated from the infant's left chest. Cough, expectoration, and fever continued and the infant was brought to the hospital.

*Examination.* The infant was well-nourished and well-developed but appeared acutely ill with marked tachypnea, pallor, and cyanosis. There was no deviation of the trachea. Dullness, flatness, and bronchovesicular breathing were elicited over the entire left chest. The right lung presented no abnormal findings. The heart was negative except for marked tachycardia.

*Laboratory Data.* Blood hemoglobin, 55 per cent; leucocytes, 32,400 per cubic millimeter (36 per cent segmented polymorphonuclear cells; 26 per cent non-segmented polymorphonuclear cells; and 44 per cent lymphocytes).

*Course.* The diagnosis of post-pneumonic empyema of the left chest was made on admission. A roentgenogram of the chest disclosed a dense shadow over the entire left lung which was attributed to the presence of a pleural effusion with displacement of the heart and mediastinal structures to the left. This was considered the result of a collapse of the lung beneath the pleural effusion. Thick purulent material was aspirated from the left chest at the level of the eighth rib in the posterior axillary line, which on culture yielded *Staphylococcus aureus*. A thoracotomy, with partial resection of the ninth rib, was then performed. A few flakes of thick pus were encountered within the pleural cavity. The left lower lobe was found consolidated. A loculated abscess cavity was opened and packed. The wound was dressed and strapped tightly to prevent collapse of the lung. The infant's condition following operation was poor. Despite a transfusion and supportive measures, the temperature rose sharply to 107.6°F. The infant died one day following the operation.

A rational explanation for the peculiar clinical picture beginning at three weeks

of age might be found in an umbilical vein infection, with formation of a metastatic pulmonary abscess, rupture into the pleural space, and empyema.

*Necropsy Findings.* The major anatomical findings were suppurative bronchopneumonia of the left lower lobe with abscess formation, peribronchial pneumonia of the left and right upper lobes, and a left serofibrinous pleuritis. Patchy atelectasis of the entire right side, acute purulent tracheobronchitis, and acute tracheobronchial lymphadenitis were also noted. Culture of the pus yielded *Staphylococcus aureus*. Microscopic examination of a routine section taken through a portion of this large abscess cavity disclosed some irregular fragments of bone, most probably aspirated foreign material, possibly chicken bone.

The heart weighed 35 grams. The parietal pericardium over the anterolateral surface of the left ventricle was adherent to the adjacent pleura. It stripped easily, however, and showed a shaggy surface covered with short fibrinous tags. The pericardial sac contained about 10 cc. of thick glary, gray-green, fibrinopurulent fluid which on smear showed many pus cells and occasional Gram-positive cocci. There were no other pertinent findings.

*Comment. Dr. Lilienthal:* Contrary to the common belief, contraction of the left chest can not be regarded as proof that an empyema did not exist. The chest is usually contracted on the side of an empyema and the mediastinum is drawn over to the side of the lesion. Only acute cases of effusion, including hemorrhage into the pleural cavity, displace the mediastinum to the opposite side.

*Dr. Klemperer:* Multiple abscesses limited to one lung with one large multiloculated cavity are atypical in common bronchopneumonia. The aspiration of a foreign body (chicken bone), however, could produce a suppurative bronchopneumonia of the left lower lobe with subsequent abscess formation.

*Dr. Baehr:* In the case under discussion, atelectasis, due to bronchial obstruction, might have contributed to pulling the mediastinum over to the side of the empyema. It is probable that before this infant was three weeks old, somebody had allowed him to suck on a chicken bone and a fragment had been aspirated into the lung.

Reported by *Joel Hartley, M.D.*

*Wednesday, February 2, 1938*

Coronary Thrombosis: Perforation of Interventricular  
Septum. Carcinoma in the Remnant of Prostatic Tissue  
Left after Prostatectomy.

*(From the Medical Service of Dr. B. S. Oppenheimer)*

*History* (Adm. 416439; P.M. 10585). The patient was a 72 year old male who was operated upon in February 1935 for a fibroadenoma of the prostate. At that time he gave a history of moderate dyspnea on exertion and some ankle edema. Following the prostatectomy he was free of genito-urinary symptoms. Three weeks before the second admission

(November 9, 1937) he was awakened from sleep by an attack of severe precordial oppression. This was his first attack of pain and lasted for about eight hours, gradually lessening. He visited the Out-Patient Department of this hospital where an electrocardiogram showed left ventricular preponderance, slight slurring of QRS complex, and T3 low amplitude. For the next three weeks he continued to have attacks of precordial oppression which were frequently related to exertion. Two weeks prior to entrance to the hospital he developed increasing dyspnea and orthopnea. An electrocardiogram in the Out-Patient Department was reported as suggestive of myocardial infarction. Blood pressure was 115 systolic, 80 diastolic. Since his operation in 1935 the patient was known to have had a blood urea nitrogen which varied between 40 and 60 mg. per 100 c. c.

*Examination.* The patient was a well-developed but acutely ill male. He was dyspneic. The lips were moderately cyanotic. The neck veins were tortuous and distended. The fundi revealed increased light reflex of the arteries and some venous compression. There were dullness, bronchial breathing, and crepitant râles over the entire left lower lobe. A systolic thrill was palpable over the entire precordium; a loud, rough, systolic murmur was heard over the aortic area; it was loudest over the lower end of the sternum. The murmur was transmitted into the vessels of the neck. The rhythm was regular. The blood pressure could only be obtained by palpation and was 90 mm. of mercury, systolic. The abdomen was moderately distended. The liver edge was firm, somewhat tender, and was felt three finger-breadths below the right costal margin. There was slight pitting edema of the lower extremities.

*Laboratory Data.* Blood hemoglobin, 54 per cent; white blood cells 14,850 (86 per cent polymorphonuclear neutrophils which showed marked toxic granulation). Blood urea nitrogen, 127 mg.; creatinin, 5.5 mg.; sugar, 110 mg. per 100 cc.; carbon dioxide, 28.5 volumes per cent. The blood Wassermann reaction was negative. A urine specimen could not be obtained. The electrocardiogram showed ventricular tachycardia, markedly elevated in lead IV, T-4 diphasic. These changes were considered to indicate involvement of the ventricular muscle due to acute coronary occlusion. Venous pressure was 23 cm., with a rise to 27 cm. following right upper quadrant pressure. Saccharine time was 34 seconds.

*Course.* The patient's condition declined in spite of the use of aminophyllin intramuscularly, Magendie, and oxygen therapy. The morning after admission the temperature dropped to 96°F. and the patient died.

*Necropsy Findings.* The entire *pericardium* was covered with a layer of shaggy, fibrinous exudate. The pericardial sac contained over 50 cc. of a fibrinosanguineous exudate. The *myocardium* of the anterior surface of the heart and apex showed the distinct yellow and red flecking characteristic of acute myomalacia. There was a marked thinning of the septum, and at a point 6.5 cm. distal to the A-V ring and 1 cm. from the anterior wall there was a small funnel-shaped perforation of the interventricular septum, 1 cm. in diameter. This opening was surrounded by necrotic, yellow, granular myocardium. The anterior descending branch of the left coronary artery, 6 cm. from its origin, showed a recent occlusion. The right coronary artery also showed considerable narrowing of its lumen, due to severe arteriosclerosis of its walls.

The other organs—*liver, stomach*, and particularly the *intestines*—showed evidence of severe stasis due to the myocardial failure.



The *kidneys* showed two processes which had produced diminution in size and parenchymal function. The left kidney was a typical small arteriosclerotic granular kidney weighing 125 gm. and showing many depressed cortical scars. The right kidney weighed 75 gm.; in addition to the granulations and scars due to arteriosclerosis (nephrosclerosis), it had a dilated pelvis, flattened calyces, and strikingly narrowed cortex. It also had many large areas of marked atrophy. This was attributed to a pyelonephritic process with renal destruction consequent to prostatic hypertrophy and associated urinary stasis.

Both lobes of the *prostate* were enlarged due to fibroadenomatous hyperplasia. The right lateral lobe, in addition, had a soft area situated within the compressed tissue surrounding the fibroadenomatous nodule, which proved to be carcinoma on histological examination. A chronic cystitis was also found.

*Comment. Dr. Baehr:* The possibility of overlooking a prostatic carcinoma has been advanced as an argument against intraurethral resection of the prostate. Here we have an instance in which a carcinoma developed in the remnant of prostatic tissue which is always left in the bed of the prostate, after removal of a prostatic adenoma by the suprapubic route.

*Dr. Master:* When a patient with myocardial infarction develops a loud systolic murmur and a systolic thrill, it usually occurs as the result of a perforation of the interventricular septum. A pulmonary embolus, however, will occasionally give identical signs. One does not usually get a perforated interventricular septum unless the right coronary artery is severely sclerotic, in addition to the occlusion of the left coronary artery. It should be stressed that when definite bundle branch block lesions are observed in the electrocardiogram, involvement of the interventricular septum should be suspected.

Reported by *M. C. Tyson, M.D.*

*Wednesday, February 16, 1938*

### Diaphragmatic Hernia or Eventration of the Diaphragm.

*(From the Surgical Service of Dr. Harold Neuhof)*

*History* (Adm. 413510; P.M. 10533). A 65 year old white male entered this hospital on September 1, 1937. He had been well until eight years before admission when he began to experience epigastric distress and pain. Following roentgenographic studies of the gastro-intestinal tract, a diagnosis of diaphragmatic hernia was made. The patient was treated by gavage, and after several weeks his symptoms abated.

In December 1934, a suprapubic prostatectomy was performed at this hospital. The patient's convalescence was uneventful. Examination of the abdomen at that time revealed no abnormal findings.

The patient remained well until about six months before admission when he began to complain of abdominal distention, gaseous eructation, and episodic vomiting. Roentgenographic examination by his physician showed the stomach to be almost completely herniated into the chest

cavity. The patient was considerably relieved by a soft diet and gavage. Two months before admission, however, his symptoms recurred, and his general condition became worse. During this period he lost twenty-five pounds in weight, and experienced almost persistent vomiting of sour-tasting, partially digested food. Throughout the two weeks prior to admission, the patient vomited nearly everything which was taken by mouth. The vomitus recently had become chocolate-colored.

*Examination.* The chest was of the emphysematous type. There was some dullness at the left base posteriorly. The heart was not enlarged; its sounds were distant and poor in quality. There were no cardiac murmurs. The rhythm was regular. The blood pressure was 110 systolic and 70 diastolic. The abdomen was scaphoid in shape. The liver and spleen were not palpable.

*Laboratory Findings.* The urine had an alkaline reaction to litmus. Its specific gravity was 1.030. Blood hemoglobin, 71 per cent. Blood chemistry: urea nitrogen, 22 mg. per cent; chlorides (as NaCl), 495 mg. per cent; CO<sub>2</sub> combining power, 82.5 volumes per cent; albumin, 3.3 gm. per cent; globulin, 1.8 gm. per cent; and total protein, 5.1 gm. per cent. The blood Wassermann reaction was negative. Roentgenographic examination of the chest showed the stomach to be completely above the diaphragm. The cardia was in its usual position; the body extended across the midline; the pylorus was on the left side of the midline. The appearance suggested a diaphragmatic hernia. A second observation six hours after ingesting the barium meal revealed that only one-third of the barium had passed through the pylorus.

*Course.* The patient's vomiting and alkalosis were controlled by the use of an indwelling Levin tube and continuous intravenous infusion. Ten days after admission a left phrenicectomy was performed in the hope that this procedure might enable the diaphragm to relax sufficiently to permit the stomach to drop back into the abdomen, and thus relieve the obstruction. There was no improvement, however. Four days later, therefore, a Witzel jejunostomy was performed for the purpose of feeding. At operation "a large defect" was found in the left leaf of the diaphragm. The stomach was drawn down and delivered into the abdomen, although there were many adhesions between the stomach and the edge of the defect. Following the jejunostomy there was considerable clinical improvement, in spite of the development of a left pneumothorax.

Four days after the second operation the patient suddenly manifested dyspnea, cyanosis, and complained of abdominal pain. The pulse rate rose to 140 beats per minute, and the temperature rose to 101°F. The following day the attack of dyspnea recurred, and a pleural friction rub became audible over the right lower chest. The pulse rate again rose abruptly to 140 beats per minute. Loud bronchial breathing was now heard at the left base, and was attributed to compression by the distended stomach. Two days after this episode, and nine days after jejunostomy, the patient had a final attack of dyspnea with cyanosis. He rapidly went into shock. His blood pressure fell to 50 systolic and 40 diastolic. The cervical veins became distended. The temperature had risen from 100°F. to 103°F. In less than an hour the patient died. The clinical impression was that death was caused by a pulmonary embolus or a coronary artery thrombosis.

*Necropsy Findings.* The lower lobe of the left lung was collapsed, flabby, and airless. There was a confluent bronchopneumonia of the right lower lobe. The remaining lobes showed atrophic emphysema. There was moderate hypertrophy of the right ventricle of the heart. There was severe myocardial fibrosis with thickening of the endocardium of the posterior portion of the left ventricle. The wall in

this area was very thin. The coronary arteries showed marked atherosclerotic thickening of their walls with narrowing of the lumina. In the left circumflex artery, two centimeters from its origin, there was an organized thrombus with an eccentric pin-point lumen. A similar picture was found in the right coronary artery three centimeters distal to its ostium.

In the left para-esophageal portion of the tendinous part of the *diaphragm* there was a pouch-like projection of the diaphragm into the thoracic cavity. The pouch measured about 12 centimeters in depth and about 10 centimeters in diameter. The rim was firm and sharp. The wall of the sac was intact and was considerably thinned. There was no communication between the peritoneal and pleural cavities. Filling the sac was the fundus and most of the antrum of the stomach, so that the larger portion of the *stomach* lay in the left thoracic cavity, although it remained intraperitoneal.

*Comment. Dr. Klemperer:* This is not a true case of diaphragmatic hernia, but rather one of relaxation or eventration of the diaphragm. In most cases of eventration almost the entire half of the diaphragm is relaxed, generally the left leaflet, and bulges up to the level of the second rib. I am unable to account for the anomaly of the diaphragm in this case, since in the usual instance the sac shows a gradual transition from muscle to fibrous tissue. In this case the entire sac was formed by a relaxed, thinned muscular diaphragm.

Reported by *Leonard E. Finkelstein, M.D.*

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Ionized Blood Calcium in Patients with Renal Calculi.* H. POLLACK AND M. REINER. Proc. Soc. Exper. Biol. & Med., 33: 432, 1935.

No evidence for an increase of ionized calcium was found in the blood of twenty-four cases of renal calculus disease.

*Choleic Acids. VI. Coordinative Valency and Isomerism. Colored Choleic Acids.* W. MARX AND H. SOBOTKA. J. Org. Chem., 1: 275, July 1936.

In continuation of previous studies of choleic acids, i.e., molecular compounds of bile acids with a great variety of organic compounds, the authors investigated choleic acids of pairs of cis-trans isomers, such as oleic and elaidic acids. They synthesized choleic acids of phenanthrene and anthracene. Various aromatic diketones formed colored, slightly soluble coordination compounds with deoxycholic acid, which may be valuable in the quantitative analysis of bile acids.

*Selective Fermentation. III. Fermentation of Hexose-Pentose Mixtures.* H. SOBOTKA, M. HOLZMAN AND M. REINER. Bioch. J., 30: 933, May, 1936.

In continuation of studies on the behavior of sugar mixtures in metabolism, xylose and arabinose were mixed with glucose and fructose. The two former have a retarding influence of the fermentation of the two latter, due to a phenomenon of "competitive diffusion." Rate and extent of diffusion was then studied for a dozen sugars with cells of various yeasts. Significant differences were observed between various carbohydrates which are constituents of important food stuffs. The new technique for studying diffusion of sugars into cells permits the differentiation of extracellular, intracellular, and chemically bound water in the cell.

*Selective Fermentation. IV. Trehalose Formation in Cellfree Alcoholic Fermentation.* H. SOBOTKA AND M. HOLZMAN. Enzymologia, I: 168, 1936.

The deficit between carbon dioxide produced, and residual reducing power in fructose and glucose fermentation with cellfree yeast maceration juice, amounts to one-half to one-third of the original amount of sugar. At the same time a highly dextrorotatory, non-reducing substance is formed whose behaviour on acid hydrolysis points to its identity with trehalose or trehalose monophosphate.

*Inhibitors of Choline Esterase.* H. SOBOTKA AND W. ANTROPOL. Enzymologia, 2 (Newberg volume): 189, 1937.

The hydrolysis of acetylcholine by choline esterase influences decisively the balance between the sympathetic and the parasympathetic nerve system.



The authors observed that various bile acids invariably cause inhibition ranging from moderate effects to complete abolition of enzymatic hydrolysis.

The nitrogenous component of toad poison, bufotenine, chemically related to the characteristic inhibitor of choline esterase, physostigmine, causes inhibition. The alkaloid, berberine, produced complete inhibition, while snake venoms from American Crotalidae inhibited the enzyme but slightly.

*Studies on Triazines. I. Reaction of Isocyanuric Ester with Organomagnesium Compounds.* H. SOBOTKA AND E. BLOCH. J. Am. Chem. Soc. 59: 2606, 1937.

By the reaction of isocyanuric ester with methyl, ethyl, or phenyl magnesium iodide, a series of 1,3,5-trimethyl-2-alkyl (or aryl)-2-hydroxy-4,6-dioxohexahydro-triazines were prepared. They permit the study of hydroxytriazines which have been proposed as a model for protein structure; the introduction of three atoms of bromine or iodine yields new products with interesting properties.

*Studies of Triazines. II. Lactim-Lactam Isomerism in Substituted Tetrahydro-triazines.* H. SOBOTKA AND E. BLOCH. J. Am. Chem. Soc., 60: 1656, 1938.

Cyclization of benzoylbiuret leads to triazines related to those studied in the first paper of this series, but with two less atoms of hydrogen. Methylation with diazomethane yields a pair of isomers representing a case of lactim-lactam tautomerism. A tetrabromo-derivative resembles the halogenated products of the first series.

*Metabolism of Sodium d-Lactate. I. Utilization of Intravenously Injected Sodium d-Lactate by Normal Persons.* L. J. SOFFER, D. A. DANTES, R. NEWBERGER, AND H. SOBOTKA. Arch. Int. Med., 60: 876, November 1937.

The intravenous injection of sodium d-lactate in doses of from 50 to 75 mg. per kilogram of body weight is followed by a considerable rise in the concentration of lactic acid in the blood, which attains its peak at the end of five minutes and returns to the control level within one-half hour.

In six of the eight subjects, the lactic acid content of the blood fell below the control level within from one-half to one hour after the injection.

In only one of the eight subjects did there occur an increase in the excretion of lactic acid in the urine after the administration of the sodium d-lactate.

No appreciable change in the carbon dioxide content of the serum occurred in any of the experiments.

In only one subject did there occur a significant rise in the blood sugar content after the injection of sodium d-lactate.

*Studies in Psoriasis. I. Lipid Partitions and Albumin-Globulin Ratio in One Hundred and Thirty Cases. II. Effect of Administration of Cholesterol (Tolerance Test) on the Lipid Partition and the Albumin-Globulin Ratio.* I. ROSEN, M.D., H. ROSENFELD, M.D., AND F. KRASNOW, PH.D. Arch. Dermat. & Syphilol. 35: 1093, June 1937.

Careful blood studies were carried out on 130 patients with psoriasis (grouped according to the duration and extent of the disease). The blood serum was analysed for total lipids, total cholesterol, cholesterol-esters, phosphorus lecithin, albumin and globulin. As control, the serum of thirty-three clinically normal patients was analysed.

The finding showed:

I. Total cholesterol in patients suffering from chronic localized psoriasis with acute exacerbation and with psoriasis of the nails only, was diminished against the norm.



II. Serum cholesterol was lowered in patients with chronic psoriasis (of more than six months' duration) according to the degree of scaling, lowest in extensive scaling. Serum globulin tended to be above the average normal range.

The 130 patients presented a grand average of  $208 \pm 28$  mg. per cent serum cholesterol, 42 per cent below average, 49 per cent within the normal range, 9 per cent above the normal average of  $228 \pm 26$  mg.

None of the other constituents showed any significant variation.

The results are entirely at variance with those of Grutz and Burger; the high values reported by those authors for total cholesterol could not be corroborated. The claims of Grutz and Burger, that patients with psoriasis show increased values for lipid phosphorus and cholesterol-esters also remain unsubstantiated.

The psoriatic process appears to show hypocholesteremia rather than hypercholesteremia. The more acute forms effect the more marked decreases, possibly caused by the mobilization of cholesterol to the affected areas.

Grutz and Burger claim that in psoriasis the cholesterol content of the blood serum does not increase after intake of cholesterol, whereas there is an increase in normal persons when cholesterol is injected. Our series of tolerance tests included ten normal patients and ten psoriatic patients. A postabsorptive sample of blood was drawn from each subject and, four, eight, and twenty-four hours after ingestion of five grams of cholesterol, dissolved in 100 grams of olive oil. The serum was analysed for the same constituents as above. The effect of the intake of cholesterol on the blood serum was extremely slight. In 84 per cent of the subjects the variation in the blood serum after the ingestion of cholesterol did not exceed 10 per cent. There was no regularity in the type of curves obtained. On the basis of this test it is not possible for the present to assume that a disturbance of lipid metabolism is present in cases of psoriasis.

*Ocular Manifestations of Malignant Nasopharyngeal Tumors.* K. SCHLIVEK. Arch. Ophth. 17: 1055, June 1937.

This is a review of thirty-eight cases of malignant nasopharyngeal tumors; five of these first consulted the ophthalmologist. Sixteen cases had symptoms referable to the eye. The eye signs are as follows: involvement of the fifth nerve, Horner's syndrome (complete or incomplete), sixth nerve, facial nerve, ophthalmoplegia interna and externa, exophthalmos, ptosis, papilledema, papillitis, optic atrophy, mass in the orbit. Two of the cases had the sphenoidal fissure syndrome, i.e. paralysis of the third, fourth, sixth and ophthalmic division of the fifth. The ophthalmologist should be familiar with this condition. When eye signs are present the tumor has already metastasized. In this group with ocular symptoms, involvement of the cervical glands was not common. Horner's syndrome is a frequent and important sign. We can evolve an ocular syndrome of nasopharyngeal tumor:—involvement of the fifth, sympathetic, and sixth nerves, either individually or together, with symptoms referable to the ear are strongly suggestive of nasopharyngeal tumor.

*Sodium-d-Lactate Blood Clearance as a Test of Liver Function.* L. J. SOFFER, D. A. DANTES AND H. SOBOTKA. Proc. Soc. Exper. Biol. & Med. 36: 692, June 1937.

The metabolism of intravenously injected sodium-d-lactate in patients with acute diffuse parenchymal disease of the liver has been shown to differ markedly from its metabolism in normal individuals. In the former group ("hepatitis," "catarrhal jaundice"), there occurs a distinct delay in the utilization of the injected salt, whereas in normals it is promptly converted into glycogen in the liver.

When the test was applied to patients with common-duct obstruction, the clearance of the lactate was observed to follow the normal pattern. The presence of dia-

betes or diffuse muscular disease apparently does not influence the utilization of the salt.

The limited investigations reported suggest that the test may have its chief value in the differentiation between extra-hepatic obstructive and non-obstructive types of icterus.

*Gonorrhea in the Female Treated by a Combined Heating Technic.* W. BIERMAN AND E. A. HOROWITZ. Am. J. Obst. & Gynec. 34: 68, July 1937.

We treated one hundred and twenty-one cases of gonorrhea in the female during the past six years, with success in one hundred and thirteen (93%). The technic consists in elevating the systemic temperature to 105.5-106.5°F. and applying additional local heat to the pelvis. Systemic temperature elevation is maintained for twelve hours, and pelvic temperature of 109-110°F. for six hours. A special type of vaginal electrode is employed in conjunction with diathermy or short wave current.

The cases treated included those with urethritis, cervicitis, salpingitis, oophoritis, and pelvic peritonitis. Treatment was administered in the acute stage as well as in the chronic phase. The results indicate the necessity for the immediate treatment of gonorrhea in women in any stage of the disease, the earlier the better, so as to limit the extent of the damage.

The average number of treatments required to eradicate all gonococci was 1.4 per patient. Pregnancy and organic disease are contraindications.

*Metastatic Panophthalmitis from Pyogenic Cutaneous Infections.* J. LAVAL. Arch. Ophth. 18: 104, July 1937.

A short resume of the various causes of metastatic panophthalmitis was given and it was noted that no cases had ever been reported where the original focus was a skin infection. Two cases were then reported, both of which were seen at The Mount Sinai Hospital. The first was that of a diabetic male with a carbuncle of the neck and metastatic panophthalmitis; cultures from the carbuncle and from the enucleated eye showed *Staphylococcus aureus*. The other case was that of a man with a furuncle of the nose which caused marked edema of the face and metastatic panophthalmitis. A culture of the eviscerated contents showed *Staphylococcus aureus* but no culture was made from the furuncle of the nose because the patient was admitted to the hospital when the furuncle was healing and the metastatic panophthalmitis had just begun.

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Manuscripts, abstracts of articles, and correspondence relating to the editorial management should be sent to Dr. Joseph H. Globus, Editor of the Journal of The Mount Sinai Hospital, 1 East 100th Street, New York City.

Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

## THE EDWARD GAMALIEL JANEWAY LECTURE I

THE SECRETIN OF BAYLISS AND STARLING<sup>1</sup>

EINAR HAMMARSTEN

*[Professor of Chemistry at the Karolinska Institutet, Stockholm, Sweden]*

In 1902 Bayliss and Starling were investigating the secretion from the papilla Vateri after the introduction of diluted hydrochloric acid into the upper parts of the intestine. As early as 1880 Rutherford had observed the flow of bile under similar circumstances. The phenomenon had been studied by Pavlov, Popielsky, and many others. It was regarded as a reflex, although the experiments by Hedon (1898), Thirloix (1892-1895), and v. Minkowsky with secretory transplants of pancreas had constituted clear evidence of a hormonal regulation of pancreatic secretion. It is characteristic that the master in the field of the investigation of reflexes, Starling, would discover the true significance of the first related phenomenon. He must have seen something, overlooked by others, which made him go out of this way, and conceive the idea—striking for those days—that through the influence of hydrochloric acid active molecules would be introduced into the blood, exciting the pancreas and the liver by a humoral way.

On the 16th of January he and Bayliss performed their crucial experiment by freeing a loop of the upper part of the intestine from all nerve connections except from those in the walls of the blood vessels and introducing a dilute solution of hydrochloric acid into it. By demonstrating the same flow of intestinal juices as when the nerve connections were intact, a new means of regulation of intestinal function had been discovered.

There seems to be no necessity for describing and enumerating all the control experiments made by Starling to confirm this discovery or the corroborative experiments of his many followers. On this occasion I shall only refer to the reviews on the subject of secretin by Still (1) and Ivy (2) in 1930, 1931, and 1934.

Bayliss and Starling never succeeded in purifying or isolating the active substance discovered by them. They called it secretin and the word "hormone" was introduced by them for secretin as a representative for a supposed whole group of similarly active substances.

For a rather long time the importance of this discovery was either not rightly understood, or it was thought that secretin could not be used for practical purposes.

<sup>1</sup> Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York City, May 24, 1938.



The methods of purifying this hormone by Ivy, Mellanby, Still, and others were followed in many respects from 1927 on by a group of workers in the Chemical Department of the Karolinska Institutet in Stockholm.

In 1933 we succeeded in preparing a crystalline salt of secretin with picrolonic acid. We found that the hormone extracted with diluted sulfuric acid from the mucous membrane of pig intestine was obtained in a mixture with proteins, lipins, and salts that was rather difficult to break up. In our first publication (3), in fact, secretin was obtained in a form soluble in benzene, due to the high phospholipin content of this preparation. It was finally necessary to introduce an extraction method (4, 5, 7) in which the mucous membrane was kept as intact as possible during violent stirring. The yield of raw material was raised about ten times by this procedure with a lower content of impurities. The second measure which made the ultimate crystallization possible was electrodialysis. This was carried out in an apparatus designed by E. Hammarsten with small and large capacities (7, 8). The secretin, being a base, was freed from the above-mentioned impurities with a yield of 90 per cent by using low temperatures and immediately neutralizing with salicylic acid. The resulting dry powder, consisting mostly of salicylic acid, obtained after concentration (at about 18°C.), took on the solubility of salicylic acid. Without going into further details I wish to mention that secretin salicylate in an impure state could be precipitated from the solution in absolute alcohol with ethyl-ether and transformed into a salt of picrolonic acid, which could be "recrystallized" from alcohol. X-ray spectra, however, failed to reveal a crystalline structure, and the activity was unaltered after many "recrystallizations."

According to our standardization method (9) on cats, this was 120 cat units but after a real crystallization in absolute water-free pyridine the activity rose to 250 cat units and remained at that level. Any amount of water in the pyridine was apt to set the base free. Strict precautions were taken to ensure a thoroughly desiccated atmosphere. Usually this picrolonate, which contained only a small amount of picrolonic acid, was transformed to the phosphate and this is absolutely stable in a dry state, just as the picrolonate is. This latter could not be injected on account of its low solubility in water. As much as 5 gm. were prepared for Ågren's thesis. The main chemical and physiological properties of such a phosphate had been established (7) but many points were cleared up by Ågren (8). It must be pointed out, however, that Ågren and I succeeded, in 1937, in digesting the crystallized secretin with an aminopolypeptidase (10) without any loss in activity whatsoever. By this digestion about 40 per cent of the amino acids constituting the secretin molecule were split off. A preparation of carboxypolypeptidase, which had previously been freed from "trypsin" by means of electrophoresis in the presence of protamin, did not exert the slightest influence on the hormone in regard to digestion or activity. According to Linderström-Lang (6) our crystallized secretin

is digested by a pepsin and enzyme extract from the pancreas, followed by complete inactivation of secretin. The attainable minimum molecular weight of secretin which is still active is therefore an open question. The crystallized secretin does not give the ninhydrin reaction (7) in spite of its content of many different amino acids (8). Ågren demonstrated a very low solubility at a physiological reaction (pH 7.4) and his measurements of the isoelectric and isotonic reactions have explained the high salt binding capacity, and the reason why Bayliss and Starling and all their followers have been unable to extract any secretin with neutral solutions. This being the only foundation for the hypothesis of "pro-secretin," to date there does not remain anything for the support of this hypothesis. By this statement I do not wish to express any opinion whatsoever regarding the mechanism of the incretion of secretin. The fact that this incretion coincides with the acid gastric contents' coming into contact with the wall of the duodenum might just as well be explained by the physiological activity of the duodenum setting in at the same time. It must be remembered that we do not know anything about the solubility of secretin in the living cells or its position there at the exact moment of incretion.

Our investigations have further demonstrated its stability in acid solution, whereas the alkaline reaction inactivates the hormone comparatively quickly. This inactivation parallels the ninhydrin reaction—a very important fact shown in Ågren's work (8). The ninhydrin reaction is inversely proportional to the activity and very strong with 100 per cent inactivation. The molecular weight of secretin was determined in Svedberg's laboratory. The phosphate investigated was homogeneous and its molecular weight 5.000 (7). Crystallized secretin behaves like a base and many of its properties in this respect have been made clear by Ågren. By further work on the pending question of its structure, van Slyke's effective methods, together with digestive experiments, should be very helpful.

Secretin is no protein in the usual sense because of the low molecular weight and the absence of an  $\alpha$ -amino group in a relation to a carboxyl group necessary for a positive ninhydrin reaction.

I would like to emphasize the thorough splitting of secretin without loss of activity (10) when an adequate catalyst—in this case, aminopolypeptidase—was used. Pepsin, trypsin, alkaline or acid reaction were also useful for splitting up the molecule but only in connection with inactivation. It may well be that many preparations, active in other respects and apparently consisting mostly of protein, could be freed from really inert protein by the appropriate method or even in some cases split into smaller molecules. We do not know, of course, if our experience with secretin can be successfully applied to other active substances, e.g., insulin or others belonging to the inseparable group of hormones, vitamins, enzymes and perhaps other active substances.

Secretin is readily distinguished by its properties from cholecystokinin

and the incretin of Nasset. The splendid work of Nasset (16), in Rochester, New York, has established incretin as a hormone with characteristic properties, both chemically and physiologically, for stimulating the secretion of enzymes in the small intestine. The three best known hormones stimulating activities in the intestine are cholecystokinin, secretin, and incretin. These three are different, and so far secretin seems to be best characterized among them. Other active substances belonging to this group influencing the blood sugar level, motility and blood pressure, blood regeneration, and substances safeguarding the mucous membrane of the pylorus and duodenum are less well known. There seems to be no doubt as to their presence or formation, however, in the mucous membrane of the pylorus and duodenum, making this region one of the hormone centers in the human body. It seems to be very important to investigate closely, the properties of these active substances, the places of their formation and incretion and the extent of this hormone region. This may easily vary in different individuals.

It is quite obvious from the experiments on cats that secretin has no other action than stimulation of the flow of bile from the liver to the gall-bladder and stimulation of the flow of pancreatic juice. A more detailed investigation has been carried out by Ågren concerning its pharmacodynamic properties (8).

The following analysis, carried out by Ågren with B. Eisler as assistant, is of special interest (11). It is well-known that atropin has no influence on the stimulation of secretin; but the inhibitory effect on this stimulation effected by direct or pilocarpin-stimulation of the vagus nerves can be abolished by ergotamine. The intestinal juices, after simultaneous injection of secretin, pilocarpin, and ergotamine have a higher enzyme activity than the juices following stimulation by secretin alone. There is no clear evidence concerning the rôle of the vagus in the physiological stimulation of the pancreatic secretion in question. The probability of a physiological inhibitory effect seems, however, to be worth considering, together with the fact, demonstrated by Ågren, of the abolishment of the above-mentioned inhibition by ergotamine.

Ågren found that the sodium salt of arsenious acid abolished all effects of secretin stimulation. This substance is commonly regarded as directly influencing secretory cells; pilocarpin might well produce spasms of the pancreatic ducts, secretin seems to be the physiological stimulant, and physiologically the enzyme production may be brought about by way of vagal stimulation. One thing, however, is certain. *Our experiments on man have clearly demonstrated the fact that secretin evokes a real formation of enzymes and not merely a "washing out" of preformed enzymes* (12).

The evidence in the literature concerning the action of secretin on man does not seem to us very satisfactory (1, 2). Up to 1934 the preparations used on man were not free from other hormones, and some of them must



have been rather toxic, as was demonstrated by Ivy on twenty-two students. Many preparations probably contained cholecystokinin, and I wish to emphasize the view expressed by Ivy as to the desirability of purification of this hormone and of secretin, if possible, in a crystalline state. The latter task was accomplished in 1933. This crystallized secretin could have been prepared in sufficient quantities for clinical purposes, in spite of the expense involved, and our purpose from the beginning has been to make the hormone available for the clinic. Only 4 to 5 mgm. are needed for a test on an adult, normally giving at least 250 cc. of bile-free pancreatic juice. The preparation, however, was too expensive. With the help of our experience regarding the properties of crystallized secretin, Ågren and I succeeded in 1934 in preparing an impure secretin after a simplified method. The activity of this preparation, prepared in our laboratory, is not more than one-fifth of that of the crystallized hormone, but it can be injected intravenously in 20 mgm. amounts without producing any effects different from those of crystallized secretin. The yield with the preparation was about 1.5 gm. per 80 meters of intestine. The injections should be made slowly, i.e., over a period of one minute. At the present time about 450 patients and controls have been injected, many of them repeatedly (from twice up to thirty times each) with this and somewhat similar commercial preparations. No ill effects have been observed in any single case, provided that the simple precaution is taken to inject a little slowly. The method of preparation, as used in our laboratory, is outlined below.

The first stages of this preparation are identical with those formerly described in 1933 (5, 7, 8). I wish to emphasize the fact that by extracting the intact mucosa of the first two meters of intestine, turned inside out, the output was raised about ten times and the amounts of impurities diminished. It seems to be a technical error to extract a ground mucosa. As in the former method, 80 meters were extracted in one batch in the specially built shaking machine. All evaporations were performed rapidly at 15°C. If the temperature is raised and the evaporation is prolonged the product is different. I do not think that it would be profitable to compare with ours any preparation of secretin obtained with temperatures higher than this one at any stage of the preparation, because of decompositions which are very easy to demonstrate. The only exception to this precaution is the boiling at pH4, to be described. Such boiling should only be undertaken at a sufficient degree of purification and under exact conditions which Ågren (8) has determined on crystallized secretin. After neutralization to pH7 the extract (evaporated to one-tenth of its volume) is precipitated by saturation with sodium sulphate. The precipitate becomes a hard cake by means of a separator after spinning at 6000 r.p.m., and is then washed first at pH7 and later at pH4. It is then placed in boiling water over a free flame for exactly one minute, and cooled to room temperature.

This whole procedure must not take more than ten minutes. After precipitation of the extract with an equal volume of alcohol, the alcohol-free solution is precipitated with picric acid, and the precipitation dried after having been freed from picric acid in the usual way (acetone and hydrochloric acid). Even at this stage there are usually indications of other active substances, and the preparation is not allergen-free. It must be ground three times in a dry state with 20 cc. of water-free methyl-glycol per each gram of precipitate. The active material can easily be precipitated from the solution in methyl-glycol by alcohol or acetone. It then forms a stable powder which can be weighed out as desired and boiled in Ringer's solution for one minute under aseptic precautions just before intravenous injection. This solution is non-allergic.

A secretin test of pancreatic function has been tried out at St. Erik's Hospital in Stockholm by Hilding Berglund, Henrik Lagerlöf and Gunnar Ågren, using this preparation (13, 14). The test as it is used at the present time can be best described by quoting from Henrik Lagerlöf's description in one of his latest publications. Before doing that I wish to point out that Lagerlöf, Ågren, and myself demonstrated that injections in the same individual (12) show a definite relation between the amount of this secretin injected and the volume of pancreatic juice secreted, as well as bicarbonate content, and that repeated injections in the same individual show a new formation of enzymes as a result of stimulation with secretin. After repeated injections of secretin the enzymes rise to the same level as after the first injection, or even higher. This signifies that secretin stimulates production of enzymes from the pancreas. *I quote from Henrik Lagerlöf's publication (15):*

"An absolute condition for a worth while secretin test is the complete separation of gastric and duodenal secretion. Such a separation is by no means a new procedure; it was at least sometimes successfully carried out in Sir E. A. Sharpey Shaefer's laboratory years ago. A further condition is the complete recovery of the whole juice secreted. Ågren and I have attempted to solve this technical problem by means of a special double tube and continuous separate delivery of the juices of the stomach and the duodenum as well as the saliva. One bore of the tube ends in the stomach, the twinbore in the duodenum. Each one on its terminal portion has several holes; three inches of the duodenal tube have none, this part is to be fitted in the pyloric region. By this procedure the recovery of the juices becomes so complete and reliable that, as an instance, the secretin now is being standardized on normal individuals as well as on cats. . . . For the diagnostic test 60 minutes' volumes are being used. Bicarbonate, diastase, trypsin and lipase are determined. Since these substances are wholly absent from the bile or present in small amounts only (bicarbonate) admixture of bile does no harm. Neither does the bile effect the enzyme activities. In the clinical evaluation of the work of the pancreas the bicarbonate and the diastase are of particular importance. Their determination is simple and accurate. The mean error of the diastase method is 2 per cent."

The same publication compares pancreatic lesions: 25 cases of pancreatitis, 4 of cancer of the pancreas, 3 with calculus, and 41 normal cases.



Without going into the details given by Lagerlöf himself, I am reporting with his permission that among the cases with clinically more or less well-established pancreatic lesions, the values for amylase were found to be normal in 7 cases, slightly diminished in 5, and clearly pathological (lowered) in 22 cases. The respective distribution of bicarbonate was 15, 6, and 11. Some of the lesions belonged to the chronic type. On the whole the acute cases seem to give the lowest amylase values without influencing the values for other enzymes as much ("dissociation of enzyme production"). In other cases the lesion gives a lowering of all values (volume, bicarbonate and all enzymes). The frequency curves of the amylase (diastase) titers are very well separated and Figure 1 is given as an example. I quote Lagerlöf again: "It is clear, even from this first pathological material,

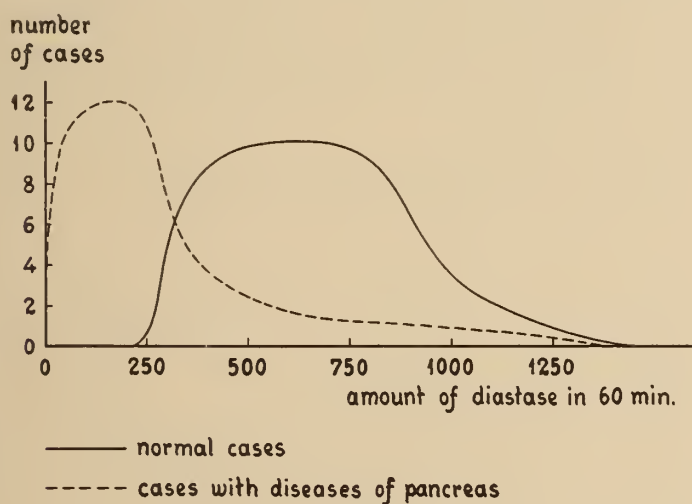


FIG. 1. Distribution curves

which has been studied by the secretin test, that alterations in function can be detected even in chronic pancreatitis, where much of the diagnosis hitherto has by necessity been guesswork."

I hope that all will understand my hesitation, however, to discuss the clinical results as these questions are far beyond my range and, besides, they have been investigated by others quite independently.

I am permitted, however, to mention some other clinical results obtained by Dr. Sigurd Elvin at St. Erik's Hospital in Stockholm and wish to express my pleasure in being able to report clinical results on behalf of both Lagerlöf and Elvin.

Elvin has investigated the possibility of using the secretin test as a means of diagnosis of disorders in the bile ducts or gallbladder. It was well-

known from Ågren's experiments on cats (1934 (8)) that crystallized secretin also stimulates a new formation of bile, and does not only wash out preformed bile. It was also discovered by Ågren and Lagerlöf in 1936 (13) on normal humans that after stimulation with secretin the bile would flow into the gallbladder, the color in the duodenal contents soon disappears, reappearing after a period of colorless flow of pure pancreatic juice. For some unknown reason, the bile soon reappears in the duodenal contents to the same degree as is characteristic for the rest secretion (yellowish to straw-colored). Elvin's material consists of 200 cases, and about 250 tests with secretin have been made on this material. All the patients had symptoms clinically suspicious of disorder in the gall-tract or of pancreatic lesions. All the cases with a clinically diagnosed disorder of the gall-tract showed an abnormal concentration of bile in the duodenal content during the secretin test. This test revealed severe pancreatic lesions in 17.6 per cent and a "dissociated function" in 24.7 per cent, i.e., some of the values for volumes, bicarbonate or enzymes were abnormally low, according to the clinical frequency curves.

Just as in the case of Lagerlöf's results, I do not wish to give any detailed report. I hope that their results will soon be published.

Comparatively large amounts of "commercial" secretin (not of crystallized secretin) have been sent to different research men on request. Ågren and I are hoping to hear about their results. The method for its manufacture is simple and not expensive. It is to be hoped that some other and still better method may be devised elsewhere. It is Ågren's and my sincere hope that this publication and lecture may do something towards the use of secretin for diagnostic purposes. The digestion of secretin, without loss of activity, to a much smaller molecule could eventually lead to a practicable preparation of active secretin in a form capable of resorption from the intestine. In that case secretin could possibly attain a therapeutic value.

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## RECENT ADVANCES IN THERAPEUTICS\*

HAROLD THOMAS HYMAN, M.D.

Progress in therapeutics results from many and varied achievements. (1) New products of chemical origin (sulfanilamide, mapharsen), and biological derivatives, such as the various hormones, have been made available for clinical use. (2) New substitutes for older drugs like cocaine and morphine have been isolated or synthesized in the effort to supply more potent and less toxic derivatives. (3) New uses have been found for familiar drugs, as in the utilization of the emetic action of ipecac in the treatment of paroxysmal cardiac irregularities. (4) Forgotten uses for familiar drugs have been revived, as, for example, iodides in goiter and mercurials for diuretic action. (5) Keener insight into deranged physiological states has clarified our understanding of the indications for potent therapeutic agents, as exemplified by the rôle of digitalis in the management of congestive heart failure. (6) New physical mechanisms, such as the vasculator, the Miller-Abbott tube, and devices for the production and maintenance of hyperpyrexia have been invented. (7) New methods of drug administration, typified by the intravenous "drip" apparatus, have altered our concepts of dosage and toxicology, and greatly widened the gap between effective therapeutics and poisoning.

\* \* \*

The therapeutics of sulfanilamide, the most important of the recently introduced chemotherapeutic agents, have been summarized before the Academy by Ottenberg (17), Marshall (13), Applebaum (1), and Blake (2). The drug is a colorless solid, conveniently supplied in tablets of 0.3 and 0.5 gram. It is soluble in water, 8 parts in 1,000. For intramuscular or intravenous use, prontasil may be obtained in 20 cc. ampoules of 2.5 per cent strength. Twenty cubic centimeters of prontasil are the effectual equivalent of one gram of sulfanilamide. An effective concentration in the blood is 4 to 10 mg. per 100 cc. attained, within three to four hours, by the daily administration of one gram of sulfanilamide orally, or 20 cc. prontasil, parenterally, for each twenty pounds of body weight. Under ordinary conditions, the total dose should not exceed 6 grams daily, though in grave emergencies 9 to 12 grams may be administered. The total daily dosage is best divided into six portions—one of which is to be administered every four hours day and night. Repeated blood examinations, by the Marshall

\* Delivered November 18th, 1938 at the Friday Afternoon Lecture Series, under the auspices of the Committee on Medical Education of the New York Academy of Medicine.

method, are advisable in the management of serious clinical emergencies. For effective treatment of urinary tract infections the concentration must be maintained at a level of 75 to 200 mg. per 100 cc. of urine of alkaline reaction and of a total daily volume approximating 1800 cc. To increase the concentration of the drug, in closed space or closed cavity infections, the 0.8 per cent sulfanilamide solution, dissolved in physiological sodium chloride, may be injected locally—as, for example, intrathecally in meningitis and into the abscess cavity, in empyema. Excretion of sulfanilamide continues approximately three days after the discontinuance of the drug.

In comparison to its potency, sulfanilamide is a remarkably non-toxic product. Its administration, however, is not without danger, due partially to individual idiosyncrasy and partially to poisoning with massive doses. Unless there be idiosyncrasy, patients can tolerate effectual doses for long periods of time. Toxic symptoms consist of nausea, vomiting, headache, slight dizziness, mental confusion, toxicodermata, and mild degrees of acidosis. The latter can be prevented or relieved by the administration of bicarbonate of soda, gram for gram, with the sulfanilamide. A purplish discoloration of the mucous membrane, confused with cyanosis, is probably due to an oxidation change in the drug, shown by Ottenberg to result from exposure to ultra-violet ray. The appearance of this discoloration, while alarming, is of no particular significance unless it clouds a true cyanosis resulting from the underlying pathological condition. The appearance of these minor toxic symptoms may call for temporary discontinuance of the drug but are of no great moment. Of graver importance are the blood changes, such as the acute hemolytic anemias and agranulocytoses that occur probably as results of idiosyncrasies. Damage to the renal and hepatic parenchyma may result in urinary changes and jaundice of ominous significance. These latter symptoms are of such potential gravity that, wherever possible, test doses should first be given to the patient and the urine, blood count, and blood serum observed before the administration of full doses. Wherever serious circumstances prevent the administration of the test dose, the patient must be repeatedly examined for jaundice or eruptions; and daily blood counts and urine analyses are mandatory. As with the arsenicals, a late toxicoderma or a chemical fever may arise, at times, after the drug has been given for a considerable number of days. Under these circumstances, the administration of sulfanilamide is to be discontinued. It is possible that the toxic symptoms increase as the result of the administration of magnesium sulphate; hence Epsom salts are contra-indicated.

The potential gravity of toxic manifestations gives the cautious and judicious physician reason to pause before employing sulfanilamide in the management of benign or self-limited infections. In the presence of severe infection, of whatever etiology, and of those inflammatory processes



that are progressing unfavorably, irrespective of indications, a vigorous trial with sulfanilamide is advisable.

Sulfanilamide is of definite and, at times, life-saving utility in the treatment of:

1. Acute hemolytic streptococcal infections, such as meningitis, peritonitis, erysipelas, septicemia, and puerperal fever.
2. Gonorrheal infections, both fresh and old.
3. Infections of the urinary tract.
4. Meningococcus meningitis and meningococcemia, with or without the simultaneous use of anti-serum.
5. Chancroid infections.
6. Undulant fever.
7. Trachoma.

The drug is of less certain but of possible value in:

1. Acute streptococcal infections, such as tonsillitis, otitis, mastoiditis, sinusitis, scarlet fever, bronchopneumonia, empyema, cellulitis, adenitis, and cholecystitis.
2. Pneumococcus infections, particularly with Type III pneumococcus.
3. Urinary tract infections with the *Bacillus proteus* and *Bacillus typhosus*.
4. *Staphylococcus aureus* infections.
5. Gangrene due to the gas bacillus.
6. Ludwig's angina.
7. Malaria.
8. Non-specific ulcerative colitis.

The drug is of dubious or no value in the treatment of:

1. The common cold.
2. Infectious arthritis.
3. Rheumatic fever.
4. *Staphylococcus* infections generally.
5. Influenzal meningitis.
6. Subacute bacterial endocarditis.
7. Friedlaender bacillus infections.
8. Putrid abscess of the lung.
9. Urinary infections with the *streptococcus fecalis*.

The use of sulfanilamide does not preclude the employment of adjuvant therapy, such as local treatment in urethritis, serum treatment in meningitis, and in meningococcal or streptococcal infections. Where a suppurative focus exists, such as an infected thrombus or a localized abscess, surgical therapy must not be neglected and should be employed in association with the drug.

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The introduction of sulfanilamide is of importance not only for itself but for the tremendous stimulus given to the field of chemotherapy.

Already newer derivatives are under investigation that may widen the therapeutic utility of the dyes. In a limited period of trial, 2(p-Aminobenzenesulphonamido) pyridine gives promise of a specific chemotherapeutic effect in the treatment of pneumococcus pneumonia.

Marshall's (14) observation on the importance of temperature for the bactericidal effect of the drug may explain the discrepancy that exists between the greater potency of these drugs *in vivo* as opposed to their simple bacteriostatic effect *in vitro*.

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Mapharsen, or arsenoxide, is another of the recently introduced preparations that may lead to great progress in chemotherapy. Originally, this product was synthesized by Ehrlich, but abandoned by him because of its toxicity. In its place he substituted the arsphenamines. Voegtlin and Smith (23), in 1920, studied the spirocheticidal action of the arsphenamines, because these preparations which, like sulfanilamide, are relatively innocuous *in vitro*, are spirocheticidal *in vivo*, though only after a period of latency. The latent period that exists between the injection of the drug and destruction of the spirochete corresponds to the period required for the conversion of arsphenamine into arsenoxide. When, in 1932, Sanford Rosenthal (20) demonstrated arsenoxide in the tissues after the injection of neoarsphenamine or arsphenamine, the hypothesis that arsphenamine owed its spirocheticidal action to arsenoxide was further corroborated. If arsphenamine is potent only when oxidized to arsenoxide and since, at most, 10 to 15 per cent of arsphenamine is actually oxidized to arsenoxide, the residual 85 to 90 per cent of the arsphenamine probably possesses little or no therapeutic efficiency. The return to Ehrlich's original preparation of arsenoxide was strongly indicated, and Tatum and Cooper (22) applied these new concepts to experimental syphilis. They reported the chemotherapeutic index for neoarsphenamine as 5—compared to 7 for arsenoxide. Raiziss (19) failed to confirm these figures.

Mapharsen, or arsenoxide, has now been made available for clinical use. It is a white powder, readily soluble in water and containing 29 per cent arsenic. It forms a stable solution and does not require neutralization. After it is dissolved in water there is a slight evolution of gas. This gas must dissipate before the solution is injected. Unlike neoarsphenamine, the drug may stand, without deterioration, for as long as two hours. The maximum recommended therapeutic single dose of mapharsen is 60 mg., containing approximately 18 mg. of arsenic. This is one-seventh the arsenic content of the ordinary maximum dose of neoarsphenamine, which contains approximately 120 mg. of arsenic in a 600 mg. dose. Unlike the arsphenamines, which must be administered slowly, the intravenous injection of mapharsen should be given rapidly lest it produce severe local arm pain.

Mapharsen seems to have certain advantages over arsphenamine in

that it never produces nitritoid reactions, and the delayed parenchymatous lesions, such as hepatitis or dermatitis, are far less common than with the other trivalent arsenicals. No death has yet been reported as directly due to mapharsen, nor any case of hemorrhagic encephalitis.

In routine use, its effect upon the clinical manifestations of syphilis and the blood Wassermann reaction are apparently equal to, if not better than, those of neoarsphenamine; however comparing the mapharsen with the original arsphenamine, the results, particularly in early syphilis, may be inferior. In Wassermann-fast cases, Chargin and Leifer (3), obtained results that were no better and no worse than those obtained with the ordinary drugs.

Sufficient time has not yet elapsed to evaluate the efficacy of the drug in the permanent "cure" of syphilis or the protective action against late cardiovascular and neuro-syphilis. The fine work of the Bureau of Social Diseases of our City Department of Health, under the direction of Commissioner Rice, Theodore Rosenthal, Walter Clark, and Louis Chargin should go far to clarify the value of mapharsen. If the later and wider experiences with mapharsen confirm the enthusiastic reports of its advocates, it will greatly simplify the technic of the treatment of syphilis and, by reducing the amount of arsenic introduced, lessen the hazards and dangers of heavy metal poisoning. Parenthetically, it is to be noted that Goldman has commented favorably on the successful use of mapharsen in the treatment of tertian malaria.

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The study of cocaine and morphine derivatives and their substitutes, illustrates attempts to produce, by purification or synthesis, new products of lesser toxicity or greater potency. In each instance, the goal is the replacement of these powerful alkaloids by derivatives or substitutes equally potent therapeutically but lacking the dangers or objectionable side-effects and the tendency to habituation. With cocaine, the problem has been solved with such signal success that the multiplicity of useful products is bewildering. Procaine, Nupercaine, and innumerable analogous preparations provide the local anesthetic properties of cocaine with a minimum of side-effect and absence of the tendency to habituation.

Similar work with morphine and the opium derivatives has met with disappointment. Through systematic alteration of the chemical structure of either the morphine or codeine molecule, numerous new drugs have been prepared. Other opium derivatives have been sought as substitutes for morphine. The goal would seem to be a product possessing the analgesic effect of morphine without the respiratory depression, obstipation, or tendency to habituation. In each instance, investigators concluded that there is at present "no substance with effective sedative or analgesic qualities which is not at least to some degree associated with a tendency to habit formation and to addiction" (Soma Weiss (24)). Seevers

(21) doubts whether there ever will be found a derivative of morphine which lacks its undesirable qualities. Pantopon, for example, may be regarded as a solution of opium alkaloids possessing, at much greater expense, the same side-effects, toxicity, and tendency to habituation as morphine. Dilaudid, though effective in doses smaller than those of morphine, is proportionately more toxic. Addiction to dilaudid, perhaps less prone to occur than with morphine, has been reported. The best preparations of opium are still the salts of morphine and codeine. The place for the newer derivatives is probably in those cases in which untoward effects have been obtained with the common alkaloidal salts. It is rare to find any appreciable difference in toxicity.

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The same lack of success that has met the attempt to produce morphine substitutes has followed the effort to produce substitutes for atropine and physostigmine. Syntropan, Novatropin, and prostigmine may be quite as effectual as the older alkaloidal preparations but they still possess to the same annoying degree the familiar undesirable effects and side-actions.

Despite the frequency with which the opiates are prescribed and administered, certain aspects of the pharmacology of morphine are misunderstood and misinterpreted clinically. There are still some physicians who withhold morphine in the treatment of congestive heart failure and pneumonia for fear of respiratory depression. This may be good pharmacology but it is bad therapeutics. There is, perhaps, no drug which can equal morphine in the treatment of acute congestive failure, particularly if there is associated pain or shock, such as occurs in acute coronary accidents. Nor must the therapist be alarmed when the respirations are reduced to 10 or 8 or even 6 breaths to the minute, as long as the circulatory condition of the patient is clinically improved and there is no evidence of disturbance in the interchange of gases. Antidotal therapy not only is not indicated, but may actually prove harmful, through excessive cerebral stimulation of an apprehensive and exhausted patient. Antidotal treatment of morphine poisoning with such drugs as atropine and caffeine can result only in the production of further alkaloidal poisoning. Therapy in morphine poisoning should be limited to artificial respiration and the administration of oxygen with or without carbon dioxide (5 per cent).

Many urologists still labor under the misconception that morphine causes anuria and are loathe to give sedatives to patients with excruciating urinary pain. It is true that retention of urine may and does occur with the administration of opiates but there has never been any evidence to indicate that morphine reduces urinary secretion. If anuria develops during the course of the administration of morphine for urinary pain the explanation is more likely to be found in a reflex due to the fundamental urological lesion, (e.g. an impacted calculus) than in the opiate.

Similarly, confusion exists as to the action of morphine on the smooth



muscle of gut and ureter. All the pharmacologic evidence points to stimulation, and all of the clinical evidence points to depression, as illustrated by the obstipation associated with the opiates. The explanation of this paradox probably rests partially in an understanding of the pharmacology of smooth muscle and partially in an understanding of the effect of the opiate on the organism as a whole. Under laboratory conditions, all evidence points to stimulation of smooth muscle and clinicians have observed increasing colic, particularly in the early moments of the opiate effect. The obstipation which occurs, despite the stimulation of smooth muscle, is probably explainable partly on the basis of sphincteric spasm impeding the onward peristaltic rush; partly on the basis of gastric retention, for the emptying time of the stomach is virtually doubled; and partly through the insensitivity of the patients to the defecation reflex.

Isoquinoline opiates used in the relaxation of smooth muscle have found new usefulness through the intravenous injection of papaverine hydrochloride in doses of from 60 to 100 mg. in the therapy of the intermittent spasm of the digital arteries in Raynaud's disease. Mulinos (16) and his co-workers by their use of papaverine in large doses, introduced intravenously, have revived interest in a preparation that had been virtually abandoned. They report an increase in the blood flow, increase in the volume of the hand, elevation of skin temperature, increase in the heat output of the skin of the finger, and dilatation of the capillary tufts. Except for some depression of the sensorium, no untoward side-effects were observed. Three injections a week gave fine symptomatic relief and this new work merits the attention of all clinicians.

The importance of the time relationship in morphine administration is little appreciated. The average dose of morphine, given subcutaneously, does not produce a maximum analgesic effect for 60 to 90 minutes; codeine, being absorbed more rapidly, is effectual somewhat sooner; and dilaudid somewhat later. Intravenous injections of all products produce maximum analgesia in approximately twenty minutes and this route of administration should be more widely employed, particularly in the excruciatingly painful catastrophes of clinical practice. Repeated subcutaneous injections of opiates, at 15 or 30 minute intervals, may easily lead to serious cumulative poisoning, whereas the intravenous introduction of the drug may give more rapid analgesia and require a smaller total dose.

The excitement that occurs as an idiosyncrasy in the administration of morphine and which simulates the so-called "cat action" in the laboratory, must be promptly recognized in the clinic, lest increased dosage produce greater excitement. It is also important to remember that morphine stimulates the spinal cord, causing increased reflexes and that this action, late in its development, is usually obscured by the earlier central depression. As a result, twelve to twenty-four hours after the administration of the narcotics, restlessness, irritability, and increased sensitivity



to pain are experienced. If, under these circumstances (which simulate the late spinal convulsions seen in the laboratory in frogs which have been given opiates) morphine is again administered, a vicious cycle is established which may ultimately lead to addiction. It is often a difficult matter to determine clinically whether the subjective complaints are due to continued operation of the fundamental pathological process or a breakdown in the morale and sensitivity of the patient. If it be the former, more opiate must be given, but if it be the latter, continuation of the opiate will lead to increasing difficulty and the eventual demoralization of the patient, as is so commonly seen in protracted but benign painful conditions, e.g. low back and sciatic syndromes.

The problem of the opiates must also be viewed in a wider perspective. Drug addiction is a disease, not a crime, and our Federal Government, in its attempts to rehabilitate the morphinists, is taking a most commendable step. Substitution of drugs, imprisonment, and drastic catharsis—the methods of the old, so-called “cures”—are stupid and futile. Imprisonment, by the introduction of the addict to the fraternity of addicts and narcotic peddlers, damns the victim for life. Mental and physical rehabilitation, which is being attempted at the Government farms, is the beginning of a newer, more intelligent, and more humanitarian era in the treatment of the addict.

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Exemplifying new therapeutic uses for familiar drugs is the use of emetic doses of ipecac in the treatment of paroxysmal cardiac irregularity. Less dangerous than digital pressure on the carotid sinus and more rapid in action than quinidine, this recent use of ipecac may prove to be “new wine in an old bottle.”

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The re-discovery of valid therapeutic observations that had fallen into unwarranted disuse is illustrated by the utilization of iodides in the treatment of goiter; the reincarnation of mercury, as in the old Guy Hospital pill, as a diuretic; and the use of opium as a so-called “cold specific” in the codeine-papaverine prescription of to-day, which is not unlike the Dover’s powder of the eighteenth century.

David Marine’s (12) epochal researches on the pathologic physiology of the thyroid gland led to the rediscovery of the efficacy of iodine in the treatment of goiter. This problem, which should be of the utmost simplicity, has been obscured by many observations and hypotheses of dubious accuracy.

Given in any form, by any route, and under any circumstances, iodine administration results in a conversion of the hyperplastic thyroid gland to the resting or colloid state. This reversion occurs whether hyperplasia of the gland is associated with the clinical evidences of cretinism,

with the familiar clinical picture of Graves' disease, or with absence of symptoms, as in the endemic goiter or 'lump in the neck.' The reversion occurs irrespective of whether the hyperplasia occurs in the adenomatous portion of the gland or in the non-tumor tissue of the gland. The adenomatous portion of the gland, functioning less actively than the non-tumor portion of the gland, will respond in a qualitatively similar, but quantitatively less marked, manner.

In each and every instance, the administration of iodine is beneficial, though naturally in long-standing hyperplasia with active congestion and vascular, as well as interstitial, changes in the gland, diminution in the size of the goiter may not be clinically apparent. Where the gland is colloidal no alteration can be anticipated unless a secondary hyperplasia has occurred as the result of repeated diminution in iodine storage.

The familiar symptoms of iodism may occur in goitrous as well as other individuals. These symptoms may consist of the usual skin manifestations or the various congestive phenomena. Over and beyond this, there are no other toxic phenomena referable to the administration of iodine. I do not believe that the administration of iodine to patients with simple goiter has ever resulted, or will ever result, in the precipitation of a crisis of Graves' disease. There is no doubt but that Graves' disease will develop in a certain proportion of individuals in a goiter belt whether or not iodine is administered, but the mass experience indicates no greater danger when iodine is administered either prophylactically or curatively in the control of endemic goiter. The development of Graves' disease in goitrous or nongoitrous individuals who have been treated prophylactically or curatively by iodine is not in causal relationship to iodine administration but a mere coincidence, and no physician, through fear of precipitating Graves' disease, should deny to his patient the use of the iodine, prophylactically or curatively, in the management of endemic goiter. Each individual, or community, presenting or threatened with endemic goiter should be given the advantage of iodine administration.

The specific effect of iodine in the treatment of Graves' disease, recently rediscovered by Plummer (18), has also been complicated by misleading conclusions. In Graves' disease, the usual response to iodine is characterized by amelioration of symptoms. In a certain proportion of patients this does not occur, or the symptoms may actually continue to increase. This latter phenomenon has been interpreted as evidence of the toxicity of iodine or an altered response due to the presence in the gland of adenomata. These explanations are made in ignorance of the natural cyclic course (10) of Graves' disease which is characterized by exacerbations and remissions. Given during the remission, iodine will demonstrate the beneficial response; given during the exacerbation, the drug may succeed only in curbing the symptoms, under which circumstance there will be no apparent improvement and if the *vis a tergo* is such that the exacerbation continues, it is

not because the iodine has become toxic or is exhibiting some unusual qualitative response, but simply because the fury of the deranged mechanism cannot adequately be stemmed. Labelling these phenomena as either iodine exacerbation or "Jod Basedow" is misleading and inaccurate and has led to timidity in the prescription of the drug for individuals who have discrete nodules in the thyroid gland or obvious adenomata. Every single patient with Graves' disease, whether the goiter is diffusely enlarged or nodular and whether or not it contains obvious adenomata, should receive the benefit of iodine therapy.

The use of iodine has been further limited by the teaching that "iodine escape" occurs and that succeeding administrations of iodine are never as useful as the first. In certain clinics, the use of the drug is limited to the few days preceding operative interference. Iodine "escape" is merely the onset of an exacerbation of the disease during the course of iodine administration. The variation in response in the same individual at different times is not due to a diminished potency of the drug but to a varying intensity of the underlying derangement. Iodine may be administered for long periods of time and may even indefinitely control the symptoms in a certain small percentage of individuals with Graves' disease. Each patient with Graves' disease should receive iodine. There should be no decision concerning operative interference, particularly in mild cases, until the efficacy of iodine therapy has been fully and completely evaluated.

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Our increased understanding of the therapeutics of digitalis is based upon a more accurate knowledge of the mechanics of congestive failure (7). The paramount indication for the administration of digitalis is congestive failure resulting from auricular fibrillation. The conduction block that is established by digitalis, allows the ventricle, through its decreased rate, a more complete systole and diastole, and the dramatic therapeutic effects of digitalization recurrently gratify the therapist. Toxicity can be avoided by observation of the ventricular rate, for rarely will digitalis poisoning be observed until the ventricle drops below 70 beats a minute. Opposed to the almost universally favorable therapeutic response that occurs in the congestive heart failure accompanying or resulting from auricular fibrillation is the universally toxic effect of digitalis when administered to individuals whose circulation is competent. The normal heart in individuals with adequate circulation responds to digitalization only by manifestations of toxicity—either diminished volume output, conduction abnormalities, such as heart block, or muscle abnormalities, such as ectopic and irregular mechanisms. Digitalis must never be administered simply because an individual has a valvular defect, or is in the throes of a pneumonia, or is to be subjected to a surgical procedure, or because of the existence of shock or hemorrhage, or the tachycardia of



Graves' disease, or simple tachycardia, for under all these circumstances it is almost a certainty that no benefits will accrue and toxic phenomena will as surely appear.

Occupying a position midway between the almost universally therapeutic effect in congestive heart failure associated with auricular fibrillation and the universally toxic effect of digitalis upon the normal heart, is the effect of the drug upon the individual with congestive heart failure and sinus rhythm. It is not to be denied that occasionally, and by a mechanism as yet not understood, digitalization may result in genuine benefit during the course of a congestive heart failure associated with sinus rhythm. The improvement will rarely, if ever, be as striking as that seen in the fibrillator, and the chance of causing toxicity is greater, since the slowing of the ventricular rate cannot be used as an index of digitalization. If the indications for digitalization are limited to congestive failure, the drug may be given immediately and with a certain anticipation of benefit in cases where there is an associated auricular fibrillation; but where there is sinus rhythm it must be given guardedly in test doses and with the knowledge that the likelihood of toxic manifestations is greater than the possibility of beneficial response. It is more advisable in the treatment of the congestive failure associated with sinus rhythm to observe the efficacy of bed rest, sedation, fluid restriction, and the removal of edema by mechanical measures or by mercurial diuresis before proceeding to digitalization.

In the presence of acute trauma to the myocardium, such as occurs during vascular accidents or in the course of the toxemias, the increased muscular irritability resulting from digitalis may induce fibrillation and thus seriously impair circulatory efficiency or cause sudden death.

The digitalis-like bodies, such as squills, strophanthus, and proprietaries, will yield nothing beyond what is obtained from a good tincture or an assayed leaf of digitalis. Nor will greater benefit be obtained from the intramuscular or intravenous administration of digitalis-like substances. Intravenous dosage presents the added danger of the production of a serious or even fatal irregularity.

The dose of digitalis (7) cannot be established *a priori* through calculations based on body weight. In certain individuals, under certain circumstances, digitalization may be obtained with considerably smaller than the estimated saturation quantities, and much larger quantities may be demanded in others. The dose of digitalis to be given to any patient is that amount required to produce and maintain the beneficial effects of the drug without the production of toxic manifestations. This amount can be calculated only by careful and repeated examinations of the patient in the light of a sure knowledge of the pharmacology of the drug. Under all circumstances, digitalization is a serious and important procedure, demanding careful and repeated observations on the part of the physician and to be regarded in every instance as a clinical experiment.

The therapeutic approach to psychiatric problems has recently benefited by two stimulating discoveries. The treatment of general paresis by hyperpyrexia is already firmly established. The introduction of the hypoglycemic state, induced by insulin, was later suggested by Sakel in the treatment of schizophrenia. Originally, it was claimed that the effect was a specific pharmacological manifestation. Remissions were reported to have been obtained in a tremendous proportion of patients and later regressions were said to be few. Confirmation of Sakel's claims was eagerly sought and work is in progress in virtually every important psychiatric center. The time is not yet ripe for the final word concerning the place of this new form of therapy in the treatment of schizophrenia, but several important facts are becoming apparent. The pharmacological mechanism of the Sakel treatment is not specific, but is rather a new and more powerful demonstration of the shock therapy in the psychoses. In ancient times, immersion in cold water and the production of a moribund state with chloroform were crude examples of a similar technic. More recently the medullary convulsive action of metrazol, a camphor derivative, seemingly produces an effect similar to that of insulin but in a simpler and less dangerous manner. The reported remissions that occurred following therapy occur exactly in the manner that Sakel described. They appear, however, to be transitory in many instances and less frequently beneficial than was originally hoped. In most clinics, psychotherapy and rehabilitation are attempted during the period of the remission as an adjuvant to the pharmacotherapy, for the shock therapy—if it accomplishes nothing else—would justify itself in rendering these patients more accessible to psychotherapy. It seems difficult, even for the experienced psychiatrist, to predict when possible success or probable failure may be anticipated. The older and experienced psychiatrists point out the frequency with which schizophrenics enter into spontaneous remission which permits some type of adjustment to the conditions of life. They also dwell upon the difficulties of diagnosing schizophrenia and the ease with which other psychoses, which are less severe and more transitory, and in which the outlook for spontaneous recovery far exceeds that of schizophrenia, may be confused with schizophrenia. They intimate that the permanent remissions may possibly have occurred in the simpler psychoses, so easily confused with true schizophrenia, and that the remaining transitory remissions are little more than the expectancy under any form of institutional therapy. Whatever may be the eventual fate of the Sakel treatment, it has at least stimulated therapy of a condition which hitherto seemed impregnable to therapeutic endeavor.

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The field of anesthesia has advanced in enormous strides. Local anesthesia by infiltration, conduction block, or local application to mucosae or denuded surfaces requires little comment.

Spinal anesthesia, in my own opinion, is comparatively too unpleasant and dangerous for continued use. The initial fall in blood pressure, the



finality of the procedure, the late disturbances in bladder and rectum, the possible transitory or permanent injury to the cord, the late paresthesias and even paralyses, the occasional danger of introduction of infection into the meninges, the consciousness of the patient, and the resultant trauma to the psyche are disadvantages that cannot be counterbalanced by the cadaveric relaxation so dear to the operating surgeon.

Basal anesthesia, on the other hand is greatly to be encouraged. Until the present, this was obtained by the use of morphine or the morphine-hyoscine combination. To-day we possess the added advantages of the use of large doses of barbiturates, of avertin with amylene hydrate, and paraldehyde.

The advantages of basal anesthesia are self-apparent. They render the psychic component of surgical intervention infinitely kinder. The patient is not exposed to the rigors of the transportation from room, through corridors, to operating room; the postoperative hours are more rapidly glossed over; the less toxic gases can be employed; the amount of inhalation gas is reduced; and much of the anguish and distress of surgical procedures is eliminated. Like all other therapeutic endeavors, however, this is not obtained without cost. If avertin be the basal anesthetic of choice, respiratory depression may develop, particularly if morphine has been administered in the course of the previous hours. Avertin cannot be used where surgery is to be performed on the lower bowel. It is contra-indicated where there are evidences of liver or kidney dysfunction, as well as in the aged and in those whose air passages cannot tolerate congestion, such as in individuals with pulmonary or cardiac disease. Upon returning from the operating room, the avertin patient needs the services of a special nurse to prevent mechanical obstruction of the air-way and the dangers due to prolonged coma. The original dosage table provided by the manufacturers of avertin is probably excessively high and most anesthetists to-day use 60 to 80 mg. per kilo rather than the 80 to 100 mg. dosage. Even then, many wise anesthetists siphon off the residual avertin once the patient becomes well-relaxed.

Barbiturates in large amounts may be used as an alternative to avertin for basal anesthesia. The oral use of Nembutal, for example, in doses of 250-300 mg., with or without morphine, and with or without scopolamine, preceding the expected operation has found wide acceptance in the hands of many surgeons. The advantages of this type of basal anesthesia are: the ease of administration, the fact that morphine can be safely employed in combination, and the greater facility with which operative procedures can be "stolen," in thyroid surgery particularly. The disadvantages are those which are inherent in all barbiturate medication. Occasionally patients may become excited to a serious degree and occasionally respiratory depression is observed. Also, the method is less applicable for emergency operations and more useful in interval operations.

The introduction of avertin has reawakened interest in paraldehyde, a useful drug too long neglected. The effectual dose of paraldehyde costs, perhaps, one-twentieth of the price of avertin. Paraldehyde has been neglected in clinical practice due to the insufficient dosage (a dose of 2 cc. is recommended in the United States Pharmacopeia). Given in doses of 15 to 60 cc. in 60 cc. of starch-water as a rectal retention enema, paraldehyde is probably the safest of all basal anesthetics—certainly the least expensive and, if exploited as well as the barbiturates and avertin, probably as useful.

The specialists in anesthesia have greatly encouraged the use of the newer gases, though many of the older inhalation anesthetics are still tenaciously used. It is surprising to observe, in spite of the dangers reported from its use, how frequently ethyl chloride is employed, particularly in children for an easy induction prior to the use of ether. Warnings to the contrary, a not inconsiderable amount of chloroform is still employed by certain of the anesthetists during the course of a tonsillectomy under general anesthesia.

For those who do not specialize in anesthesia, and where apparatus is either not available or not understood, ether is still the anesthetic of choice, for with a gauze mask and an ether can, a competent and safe general anesthesia can be administered by any physician worthy of his training. The use of ethylene, cyclopropaine, and nitrous oxide with oxygen lies distinctly within the province of the specialist. These require complicated apparatus and their administration is a matter too technical for the tyro. Administration of nitrous oxide for tooth extractions by our dental friends, holding the mask with one hand and forceps with the other, has always been a spectacle that fills me with terror and alarm.

The choice of the more complicated inhalation anesthetics should always be left to the expert anesthetist. For the majority of simple and brief procedures, particularly if a basal anesthetic has been administered, nitrous oxide will prove satisfactory. For longer procedures, or for greater relaxation, ether, ethylene, or cyclopropaine may be employed, in different stages of the procedure depending upon the decision of the anesthetist. The tendency of cyclopropaine to cause cardiac irregularity has rightly alarmed many anesthetists but those familiar with its use are less fearful. It is their experience that stopping cyclopropaine and "flooding" with oxygen is sufficient to relieve the symptoms.

The problem of obstetrical anesthesia is extremely controversial. The majority of obstetricians to-day employ the barbiturates with or without scopolamine in one form or another particularly in hospital deliveries. The general usage seems to be the administration of 250 to 300 mg. of Nembutal, orally or rectally, either at the beginning of active labor or when the patient requests the drug. This is followed shortly by the subcutaneous administration of 0.00025 mg. of scopolamine. There then follows a slight

delay in the progress of labor and a mild or considerable amount of motor excitation and ataxia that may be transitory or prolonged, depending upon individual idiosyncrasy. The Nembutal is repeated in doses of 90 to 180 mg. every three to four hours, if necessary, and one more repetition of the scopolamine is permissible. In the second stage of labor, particularly if there is marked excitation, gas-oxygen anesthesia is used for the induction and full ether or cyclopropaine for the actual delivery. This type of management requires the constant presence of skilled nursing aid as the majority of women show motor excitement. It is the opinion of experienced obstetricians that this type of analgesia results in a somewhat greater loss of blood, a somewhat more prolonged labor, and a transient and apparently harmless asphyxia of the infant.

Those who oppose the use of large doses of barbiturates, emphasize the unpleasant side-effects on mother and fetus, which are certainly more prone to occur in the hands of those obstetricians who, on promise of completely painless child-birth, administer as much as double the amounts suggested above.

The use of the barbiturates has, seemingly displaced rectal ether, but rectal paraldehyde is employed in some clinics with reported success. Pharmacologically, paraldehyde would seem to be a much safer preparation, provided its efficacy is equally well-established.

Many obstetricians still prefer to use gas-oxygen, intermittently, during the latter part of active labor, with full anesthesia when dilatation is complete and the head is controlled. This is an exceedingly expensive procedure, to say the least, since it requires the constant presence of a skilled anesthetist and the total amount of gas that must necessarily be used is not inconsiderable. While morphine could be administered during the course of the inhalation anesthesia, its use is best avoided with the large doses of barbiturate.

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The introduction of many new physical modalities has opened new avenues for therapeutic endeavor. The Miller-Abbott tube (15) is of incomparable value in the decompression of the small bowel where there is distention due to ileus or mechanical obstruction. The vasculator provides at least symptomatic relief in the treatment of peripheral vascular disease. The production and maintenance of hyperpyrexia is of firmly established value in the treatment of gonorrheal arthritis and general paresis.

\* \* \*

The intravenous drip (8) has greatly simplified and improved our methods of treatment in many diverse medical and surgical conditions. When it was demonstrated that the rapid intravenous introduction of pharmacologically active or inert chemicals, drugs, and biological fluids could give rise to alarming circulatory and respiratory symptoms, usually transitory



but at times fatal—a syndrome best described as “speed shock” (5)—it became apparent that intravenous medication and infusion must be regulated so that the rate of speed was controllable. With the velocity regulated by means of the visible drip, it was shown that the slow intravenous introduction of even the most highly toxic substances such as anaphylatoxin and histamine could be accomplished with impunity, provided that the rate of injection was reduced to 2 to 5 cc. per minute. Untoward reactions, such as the so-called “nitritoid crisis,” the anaphylactoid phenomena, the non-specific fall in blood pressure that occurred when various drugs, such as digitalis, were given intravenously, sudden deaths during the course of infusion and direct transfusion, and even anaphylactic shock itself, could be abolished by reducing the rate of flow.

The intravenous drip also has the advantage that in a single procedure (9) the patient can receive daily 3 to 5 litres of fluid and sufficient carbohydrate and saline to meet metabolic needs. Citrated blood can be added without the patient's knowledge. Sera may be administered in tremendous doses with little or no danger of reaction. Medications can be added directly to the reservoir or, for more rapid administration, injected into the rubber tubing connected with the needle. With a little technical skill and care, the drip runs readily for twenty-four to forty-eight hours. This technic has been so eminently satisfactory that it has rendered obsolete the painful subcutaneous clysis and the complicated methods employed for direct transfusions. In 1932, at The Mount Sinai Hospital, for every three intravenous sets that were ordered, two clysis sets were prepared. To-day the proportion is twenty to one, and those clysis sets still employed are for the most part used by the pediatricians, though Schick and Karelitz, following our original work, have successfully applied the technic of the intravenous drip to infants and children.

In the surgical clinics (11), the drip is used both prophylactically and supportively. It is used prophylactically in all formidable surgical procedures—e.g., subtotal thyroidectomy for Graves' disease, extensive resections of the stomach and intestines, hepatic and renal surgery, all inflammations of the peritoneum, in surgery of any type on diabetics or individuals with hemorrhagic disease. It has been used therapeutically in the various complications that follow surgical procedures, such as persistent nausea and vomiting, hemorrhage and shock, abnormalities of urinary secretion, sepsis, gastric dilatation and ileus, and especially traumatic surgery.

In internal medicine, the drip is employed in all metabolic disorders associated with nausea, vomiting, or ketosis; in states of dehydration, such as occur with persistent or toxic vomiting, or persistent diarrhea; in all types of hemorrhage and hemorrhagic diatheses; in all toxic and comatose states where the fluid and nutrition requirements of the patient must be met; in all of the infectious diseases where the repeated or constant introduction of serum is advisable and in all types of poisonings.

The use of the intravenous drip has modified our conception of the toxicology of many important drugs. Many of the dangers in chemotherapy can be averted if the non-specific accidents are eradicated. Potent therapeutic agents can be administered by means of the intravenous drip in doses far greater than previous workers dared to attempt. These achievements make possible, without serious damage to the cells of the host, the optimum in chemotherapy. To illustrate this, early syphilis has been treated by massive doses of arsphenamine (4). Twenty-five patients were given an average of 4 grams of neoarsphenamine over a period of five days—or an average dose of 0.8 grams containing 160 mg. of arsenic. The usual febrile, neuritic, and toxicodermic manifestations were observed, but there was neither a nitritoid crisis nor any evidence, early or late, of significant renal or hepatic damage. The excretion of arsenic proceeded in a rapid and favorable manner and the clinical manifestations of the syphilitic infection cleared with great rapidity. The blood serology responded more slowly but was usually negative by the third or fourth month. Though no further therapy was administered to any of these patients, such of them as could be followed over a period of five years (6) remained serologically negative and symptom-free, with normal spinal fluids and normal teleroentgenograms—demonstrating, at least, that it was possible permanently to cure early syphilis by the massive dose method in less than one week of therapy. This method is still in an experimental phase and far too hazardous for routine use. It gives promise, however, of a technic for the complete eradication of the greatest of the social menaces; it provides a weapon by which public health officials can completely control the disease. On a larger scale, these experiments indicate the necessity of reviewing and revising all of our concepts of toxicology and may, particularly with the newer chemicals that have been recently introduced, greatly widen the applicability of chemotherapy.

\* \* \*

The reporting of these therapeutic advances is a privilege made manifoldly more precious through contrast with the ominous events of our troubled world. It is a point of particular pride to note that, with a few isolated exceptions, all there is to relate of man's continued efforts toward the prevention and alleviation of the ills of his fellows, emanates from the universities, privately endowed hospitals and institutes, the civic, State, and Federal agencies of our great democratic government.

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## PULMONARY ATELECTASIS AND PNEUMOTHORAX FOLLOWING LAPAROTOMY

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The development of spontaneous pneumothorax as a postoperative pulmonary complication is a rare event. Dorwart (1) was able to collect eight cases from the literature. Two of these followed tracheotomy, five followed operations for goitre, and in one case the type of operation was not mentioned. He adds a case of his own, one of spontaneous right-sided pneumothorax occurring eleven days after a right heminephrectomy through a lumbar incision; spinal anesthesia was used. The patient made a complete recovery. Dorwart states that it is the first such case recorded after an abdominal operation. Tod and Warin (2) reported a case of spontaneous pneumothorax with the onset of an induced labor. The patient, however, had active pulmonary tuberculosis and died within a few minutes of the accident. Phillips, Waldron and Vanvant (3) have recently reported the occurrence of bilateral pneumothorax and extensive subcutaneous emphysema complicating a subtotal gastrectomy for duodenal ulcer. The patient received gas-oxygen-ether anesthesia. The subcutaneous emphysema was noted at the end of the operation, a partial right-sided pneumothorax the following day, and a partial left-sided pneumothorax eleven days later. Their patient recovered completely.

Of these eleven cases, seven followed operations in the neck where it is conceivable that there may have been direct pleural injury. In the obstetrical case the lung pathology was such that the occurrence of spontaneous pneumothorax needs no special explanation. We find, then, just two reported cases of spontaneous pneumothorax following operation in which it is unlikely that any direct pleural damage occurred during the operative procedure. (In the kidney case the pneumothorax developed eleven days postoperatively and therefore it is improbable that there was pleural injury during the operation.) The rarity of the accident, we feel, justifies this report.

### CASE REPORT

*History* (Adm. 422324). The patient was a forty-two year old housewife with a seventeen year history of right upper quadrant pain, nausea, and vomiting. Icterus accompanied some of these episodes. She suffered occasional precordial pain on exertion, relieved by rest. There was no history of pulmonary disease.

*Examination.* The patient was a moderately obese female, not acutely ill. Her heart and lungs presented no abnormality. There was slight right upper quadrant

tenderness. Blood pressure was 150 systolic and 105 diastolic. Wassermann reaction was negative. Blood urea N., 10; sugar, 85; icteric index, 2; cholesterol, 300; ester, 77. A flat plate of the abdomen revealed no gall stones. Electrocardiogram showed left ventricular preponderance and moderate slurring of the QRS complexes.

Under avertin, gas-oxygen-ether anesthesia, laparotomy was performed and a chronically inflamed gall bladder, containing numerous *facetted* stones was removed. The common duct was found to be dilated but upon exploration no stones were found. A "T" tube was inserted into the duct and the abdomen was drained and closed in layers.

While the patient was reacting from the anesthesia, she coughed considerably, became moderately cyanotic and had a great deal of mucous in her pharynx. The cyanosis disappeared after a few hours but the cough persisted. With the exception of the troublesome cough and the usual abdominal discomfort following laparotomy, her course was not remarkable during the next two days. There was then a slow onset of dyspnea and cyanosis. The chest was resonant throughout but there was some diminution of breath sounds at the right apex. The chest findings on the fourth day were more extensive. There was impaired resonance over the entire right chest with diminished to absent breath sounds over the right upper lobe and distant bronchial breathing over the lower lobe. There was no mediastinal shift. It was felt that there was partial atelectasis of the right lung. The temperature never rose above 100.8°F. The following day the pincettes were removed from the skin and later that day a superficial wound dehiscence occurred which was strapped with adhesive. A therapeutic problem now presented itself as to whether to inhibit the cough to protect the wound, or favor it to permit the expulsion of the mucoid plugs that were probably causing the atelectasis. On the sixth day the right chest became resonant posteriorly and on the following day there were tympany and absent breath sounds over the entire right chest. Bed-side X-ray examination showed a right pneumothorax occupying 50 per cent of the right pleural cavity, with some mediastinal displacement to the left.

The patient was given sedatives and kept on the right side as much as possible. On this regime the pneumothorax gradually diminished in size. There was a low grade fever which varied slightly above and below 100°F. A small pleural effusion appeared at the right base, but this was reabsorbed without aspiration. X-ray examination of the chest eight weeks after the operation revealed moderate thickening of the pleura over the right lung but no other abnormality.

#### COMMENT

Castex, Mazzei, and Vaccarezza (4) made roentgenographic and pleuroscopic studies and state that subpleural blebs are quite different from emphysematous bullae. They are small to moderate in size, located just beneath the pleura, and are formed in the pleuro-pulmonary tissue whose connective tissue is altered by previous scar formation, malformations, or circulatory disturbances. The underlying lung is healthy or only slightly altered. These authors stress the importance of effort as a decisive factor in the causation of such blebs. It was felt by the service and by the chest consultant that the pneumothorax in this case resulted from the rupture of such a bleb. The same persistent cough that caused the wound separation was considered to be the force that caused the rupture of the bleb, since with each cough there is a preliminary rise in intra-bronchial pressure against a closed glottis.

There is another factor to be considered. In the case reported by Dorwart (1) the pneumothorax was also preceded by pulmonary atelectasis. His explanation of the pathological physiology involved seems worth repeating and checking with our case. He argues that it is known that atelectasis lowers intrapleural pressure and usually the mediastinum is shifted toward the atelectatic side. If, however, the mediastinum is fixed, a still greater negative pressure is developed. This pressure is exerted on any portion of the lung that is still aerated causing emphysema and even rupture of that portion. It is as though one would compress one-half an air-filled rubber balloon so that the remaining half would have to take up all the air formerly held by the entire balloon. Of course rupture of the aerated portion of the lung neutralizes the negative pressure that had developed as a result of the atelectasis. In our case no mediastinal shift toward the right could be made out by several observers on physical examination of the chest prior to the development of the pneumothorax. The persistent cough, as mentioned above, also added to the strain on the still expanded portion of the right lung, by creating a still greater difference between the intrapleural and intra-alveolar pressures. Though a subpleural bleb may have been present prior to the operation, it seems quite possible that the process mentioned above is adequate to have caused a bleb as well as its subsequent rupture.

#### SUMMARY

A case of spontaneous pneumothorax occurring seven days after cholecystectomy is presented and an explanation is offered for the sequence of events observed.

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## THE EFFECT OF HYPERTHERMIA ON VITAMIN C IN THE BLOOD PLASMA\*

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The relationship of Vitamin C\*\* to disease has been discussed extensively in the recent literature.

Bullowa et al. (1) and Gander and Niederberger (2) have reported that there is a marked deficiency of Vitamin C in the blood plasma in patients suffering with acute pneumonia. Moreover, Hasselbach (3), in an extensive study, found that there is a marked decrease in the Vitamin C in all febrile and destructive forms of tuberculosis. Abbasy, Harris and Hill (4), investigating a series of seventeen "active" cases of osteomyelitis, stated that there was "an apparently increased usage of the vitamin during the infective process." A lowered level of Vitamin C has been found in other diseases. Finkle (5, 6) has made such observations in determining the value of Vitamin C in the urine of patients suffering with vascular diseases.

In a yet unpublished series of observations on thirty children who manifested various types of acute infections, accompanied by fever, with respiratory infections predominating, it was found, in agreement with the investigators mentioned, that there was a definite diminution in the available amount of Vitamin C in the blood plasma; the average range varying from 0.35 to 0.90 mg. per cent, the reduction being approximately 50 per cent.

What are the factors involved in the mechanisms which result in the diminution of Vitamin C in blood plasma during acute infections? One of the most conspicuous features of acute infection is fever. In fever due to bacterial invasion it is difficult to segregate the different factors responsible for the rise of temperature. The most readily available method for studying the effects of high temperature is the production of artificial fever induced by the use of the hyperthermia cabinet.

Vitamin C determinations were made on nineteen patients (Table I) suffering with various infections, such as gonorrhea, eczematoid dermatitis, multiple sclerosis, etc. All of these patients were subjected to hyperthermia for the treatment of their ailment.

\* Read before the Eastern Section of the American Physiotherapy Society, April, 1938.

\*\* The Vitamin C for Standardization of dye substance was kindly supplied by Hoffmann-LaRoche, Nutley Park, N. J.

TABLE I  
*Vitamin C estimations on nineteen patients treated with induced hyperthermia*

CASE NO.	DIAGNOSIS	DATES TREATED	TREATMENT, HOURS	CUBIC CENTIMETERS OF WATER		TEMPERATURE RANGE °F.	VITAMIN C ESTIMATION, MG. PERCENTAGE		GAIN OR LOSS	ONE HOUR AFTER TREATMENT
				Intake	Output		Prior to treatment	Immediately after treatment		
1. B. ....	Asthma	5/19/37	5	1,500	None	104-105	1.00	0.95	-0.05 (5%)	0.75
2. D. ....	Multiple sclerosis	5/10/37	5	2,500	None	103-105	1.57	2.61	+1.04 (66%)	1.89
		5/10/37	4	2,400	180	104-105	2.09	1.67	-0.42 (20%)	2.19
3. L. ....	Neurodermatitis	5/ 8/37	2	1,000	90	100-101	1.67	2.09	+0.42 (25%)	1.73
		5/11/37	2	900	?	100-101	1.77	2.09	+0.32 (18%)	1.83
4. A. H. ....	Neurodermatitis	11/ 8/37	1½	2,000	None	101-103	2.44	2.95	+0.51 (21%)	2.32
5. B. G. ....	Cervicitis	11/29/37	12	7,360	300	105-105 <sup>a</sup>	1.24	1.57	+0.33 (27%)	1.34
6. P. ....	Chorea	5/11/37	5	2,000	None	105-106	0.73	1.15	+0.42 (57%)	0.62
		5/17/37	5	2,100	None	105-106	0.86	1.12	+0.26 (30%)	0.71
7. Y. ....	Arthritis and colitis	10/ 9/37	2	4,000	600	101 <sup>8</sup> -104	1.94	2.19	+0.55 (34%)	2.17
8. D. ....	Neurodermatitis	10/26/37	2	800	120	101 <sup>2</sup> -102 <sup>8</sup>	2.85	3.97	+1.12 (39%)	2.84
9. W. ....	Dermatitis	11/12/37	11½	1,000	None	100-101	1.39	1.98	+0.59 (12%)	1.54
10. G. ....	Cervical arthritis	6/30/37	12	2,600	210	105-105 <sup>4</sup>	2.56	3.78	+1.22 (48%)	2.47
11. W. G. ....	Arthritis	6/30/37	12	3,900	300	105-105 <sup>8</sup>	2.41	3.66	+1.22 (50%)	2.53
12. R. ....	Dermatitis	1/10/38	2	2,000	None	101-102	0.69	1.01	+0.35 (51%)	0.74
13. G. ....	Neurodermatitis	5/20/37	2 2½	2,000	None	102-102 <sup>6</sup>	1.45	2.25	+0.80 (55%)	2.15
		6/ 8/37	2	1,000	150	101-102	1.65	2.61	+0.96 (58%)	1.84
14. C. ....	Dermatitis	5/ 8/37	2	1,500	None	101-102	0.83	1.88	+1.05 (125%)	1.12
		5/11/37	2	1,200	None	101-102	1.36	2.19	+1.83 (61%)	1.42
15. H. ....	Dermatitis	1/ 6/38	1½	1,030	None	101-102	2.08	3.47	+1.39 (67%)	2.24
16. B. ....	Malta fever	5/12/37	5½	3,000	360	105-106	0.72	1.41	+0.72 (100%)	1.12
17. N. G. ....	Arthritis	5/15/37	5½	3,000	180	105 <sup>8</sup> -106	0.73	1.25	+0.52 (71%)	0.83
18. T. ....	Cervicitis	5/29/37	5	2,600	None	104-105 <sup>6</sup>	0.82	1.51	+0.69 (84%)	0.92
		1/12/38	12	4,500	None, vomited (210)	105-105 <sup>6</sup>	1.82	3.97	+2.15 (118%)	2.17
19. T. ....	Multiple sclerosis	6/15/37	4	1,000	None	103-101	1.01	3.01	+2.0 (200%)	1.17

The patients were prepared to receive hyperthermia as follows. A saline enema was given at least one hour prior to therapy. Breakfast consisted of tea and toast. Before the patient was placed in the cabinet, 2 cc. of blood were withdrawn from an antecubital vein and immediately oxalated. With the patient in the hyperthermia cabinet, the temperature was raised gradually to a height deemed necessary for treatment. The patients were kept in the cabinet for varying periods of time ranging from one to twelve hours. The temperature ranged up to 106°F. Water was offered freely. The fluid intake varied from 800 to 4500 cc. Immediately after the patient was taken out of the cabinet, 2 cc. of blood were withdrawn and oxalated; this was repeated within one and two hours following cessation of hyperthermia. Hemoglobin estimations, employing the Sahli technique, were done in ten patients just prior to commencement of hyperthermia treatment and immediately following it.

Vitamin C determinations on the oxalated blood were done immediately following withdrawal of blood according to the Farmer-Abt modification of the Tillman-Hirsch method of titration using the dye substance di-chlorophenol-indo-phenol, the end point being the production of a pink coloration which lasted for at least thirty seconds.

Vitamin C estimations of the blood plasma in this series of patients were found to be raised up to 100 per cent above that level found prior to hyperthermia. However, the determinations made one hour after the patient was removed from the cabinet showed a marked fall, and in the majority of instances the level reached was approximately the same as that found previous to fever treatment. The estimations made two hours after cessation of cabinet treatment showed no appreciable changes in Vitamin C over that found at the end of one hour.

#### COMMENT

The first factor which must be considered is that of dehydration. It is apparently of negligible significance, since the studies of Bierman (7) demonstrated that the effect of hyperpyrexia is a relative leukocytosis but causes no appreciable fluctuation in the red blood cell count or the hemoglobin content. In my studies there was no change in the hemoglobin estimates in the ten patients examined.

A decrease in the available amount of Vitamin C immediately following hyperthermia was anticipated. The fact that there was an increase was surprising. However, one must consider that artificial fever produced in a hyperthermia cabinet may be unlike fever produced by true disease.

The following concept with reference to the Vitamin C figures obtained in this study may now be advanced. To begin with, the patients prior to the treatment with artificial fever had no Vitamin C deficiency and maintained an equilibrium between the Vitamin C in the tissue cells and that in the blood. With an increased utilization or destruction of Vitamin C

during high temperatures, the blood plasma, having lost its Vitamin C, may mobilize its reserves by calling on the tissue cells for this Vitamin, and attempt to replenish the diminished Vitamin C in the blood plasma. This could explain the figures found in my study immediately after the close of the hyperpyrexia treatment. It is interesting to note that as early as one hour later, the amount of Vitamin C in the plasma had returned approximately to the original level.

#### SUMMARY

In the majority of the cases treated with hyperpyrexia there occurs an increase ranging to 100 per cent in the Vitamin C level immediately following such treatment. This increase was also noted in the five patients who received one or more additional hyperpyrexia treatments. In almost all of these patients the Vitamin C level returned to its approximate normal, one hour after cessation of hyperpyrexia treatment.

No clear relationship could be noted between the height of the temperature and fluctuation of Vitamin C concentration.

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## THE BULGARIAN TREATMENT OF POST-ENCEPHALITIC PARKINSONISM<sup>1</sup>

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Since 1926, Ivan Raeff, a plant collector in the Bulgarian village of Chipka, has achieved local and subsequently European fame by his successful treatment of Parkinson's disease. The original treatment of Raeff makes use of four different medicinal packages, the analysis of which reveals that No. 1 contains radix belladonna; No. 2, carbo animalis; No. 3, pills consisting of bread dough, sawdust and nutmeg; and No. 4, calmus root.

Rather obscure directions accompany these four packages: 30 gm. of belladonna root (No. 1) and one powder of No. 2 are boiled in 600 cc. of white wine for ten minutes. This decoction is cooled, filtered, and kept in tightly closed bottles. According to the patient's age, one-half to three tablespoons of the decoction are given in one dose every twenty-four hours, after the first sleep during the night. According to Raeff, the patient must be aroused for this medication. Critical reactions may occur in the beginning of the treatment, following the medication, and lasting for only a few hours. Such a crisis usually manifests itself by delirium, hallucinations, or incoherent speech; it may be counteracted by feeding boiled milk. If these crises are very violent or do not disappear after several days, Raeff advises decreasing the dose.

The instructions further state that one of the pills, No. 3, should be taken every morning before a breakfast consisting of hot milk or tea. A pea-sized portion of calmus root, No. 4, is to be chewed six to seven times a day, and the mouth subsequently rinsed. Cod liver oil is recommended by Raeff for children, and exercises for every patient. Constipation is to be counteracted by castor oil or other means. No other medicines or injections are permitted during this treatment. In the diet, meat should be avoided, except for white meat. The mixed diet should consist chiefly of eggs, milk, butter, cheese, vegetables, fruits, rice, olives, cakes, and candies. Spices, alcohol, coffee, and tobacco must be eliminated. The patients are advised by Raeff to sleep on the right side, and, if this is not possible, on the left, but not on the back. During the hot summer season the patient should bathe after lunch for ten minutes in water warmed by the sun.

<sup>1</sup> Read at the Neurological Conference of The Mount Sinai Hospital on April 10, 1939.

Most of Raeff's directions are obviously ridiculous, although they may have some psychotherapeutic significance. This will be discussed later. There is no question, however, that the Bulgarian belladonna root, or belladonna root in general, is the cardinal point of this treatment. Nevertheless, a critical view of the other factors may be worth while; not all of them can be unconditionally discarded.

The charcoal of power No. 2 seems to be superfluous. By adsorption it may decrease the alkaloid content of the decoction, perhaps completely adsorb it and may render the preparation ineffective. The gastro-intestinal tract, at any rate, will not benefit much from the charcoal. Pills No. 3 are mere phantasy or deception. The chewing of calmus root counteracts, to a certain extent, the dryness of the mouth due to the atropine effect, but is not superior to other means.

Exercises and the elimination of toxic substances, such as tobacco, alcohol, and coffee, are as important in Parkinsonism as in any other disease of the nervous system.

The dietetic regimen, in my experience, has no special virtue. It is possible, however, that dietetic restrictions may have a psychotherapeutic effect.

The sleeping position of the patient, the peculiar bathing ceremonial, or the administration of the medicine after the first sleep, as devised by Ivan Raeff, deserve no serious discussion.

The Bulgarian treatment, as a clinical and scientific problem, may be reduced to the administration of belladonna root extract, exercises, perhaps diet, and probably psychotherapy to replace some of Raeff's mysterious directions.

The important question is whether the Bulgarian treatment offers anything new therapeutically. Various alkaloids of the belladonna group have been used for decades but without encouraging or lasting results. This hopeless situation, however, was changed by Roemer (1), Kleemann (2), and others who, as early as 1930, introduced the treatment with massive doses of atropine. Their clinical investigations were based upon Bremer's (3) observation that post-encephalitic Parkinsonians generally show a very high tolerance to atropine. Bremer found that 15 mg. or more a day could be administered before toxic manifestations appeared. Roemer and Kleemann treated post-encephalitic Parkinsonians with massive doses of atropine, 15-45 mg., in one case even up to 120 mg. a day, with striking results which have been corroborated by numerous authors in other countries. The very disagreeable by-effects of atropine, however, prevented the general acceptance of this therapy. Among them, the dryness of the mouth and blurred vision were less alarming than the severe damage to the gastro-intestinal tract with megacolon formation, as reported in the literature (4). Sometimes, there were fatal results from the protracted administration of high atropine doses.

Compared to the atropine regime, the Bulgarian treatment is an advance in therapy. What is new is the use of belladonna root instead of belladonna leaves, and the use of a natural compound instead of single alkaloids. The progress lies first of all in striking clinical results. The results are superior to those with high atropine doses, and are achieved by far smaller doses of alkaloid. The average daily dose in the Bulgarian treatment is three milligrams of total alkaloids, while at least 15 mg. are required in the high atropine dose treatment. Consequently, fewer by-effects occur and severe damage, as, for instance, megacolon formation, is less to be feared and actually has never been observed with the Bulgarian treatment.

Ivan Raeff deserves credit for this progress in the therapy of post-encephalitic Parkinsonism. He died last year, and probably would have been forgotten if the Queen of Italy had not become interested in encephalitis and endowed a special encephalitis hospital in Rome. There, after 1935, the method was studied clinically and pharmacologically by Pane-grossi (5) and Antolini-Frugoni (6). Several papers on this subject were subsequently published in Germany (7-12), Austria (13), France (14-16), Belgium (17), England (18), and Switzerland (19). One of the most impressive is the publication of von Witzleben (7).

Different decoctions and extractions have been used by different clinicians. Raeff's original wine decoction was not stable and varied in its alkaloid concentration. Overdosage might produce the "crises" such as were mentioned in Raeff's directions. Cold extractions by maceration or percolation were used with various solvents. They are stable and seem to be somewhat more effective than the decoction.

No unanimity of opinion exists as to the best belladonna root. Several workers prefer definitely the Bulgarian belladonna root growing in the region about Chipka. Others report having seen identical results with German, Belgian, and English roots. There is no question that different climate and soil, and different age and time of harvest of the roots may influence their alkaloid content and composition, as is known to be the case with digitalis leaves. But by proper titration the alkaloid content of extractions of root from different sources can be made uniform. Practical experience has proved that roots of similar alkaloid composition, and consequently of the same efficacy, can probably be found in almost every country. We interchanged extracts from original Bulgarian and certain American belladonna roots in the same patients. The difference was equivocal. But undoubtedly, too, there are roots which vary in effectiveness.

Up to this time more than 2000 post-encephalitic Parkinsonians have been treated in European countries with various extracts of belladonna root. Excellent results were unanimously reported. According to some investigators up to 80 per cent of the patients could go back to their former employment. Knowing how much influence psychotherapy has in these

patients most of whom are desperate, we must be particularly cautious and critical. The overenthusiasm which is expressed in some publications, for instance in Panegrossi's, unconsciously labels the investigators as psychotherapists. Most of the patients were hospitalized in particularly beautiful institutions. That meant to most of them a change from poor, crowded, exhausting, and uneasy conditions to sumptuous, quiet environments. Previously criticized or carped at within the family, or even mistaken for hysterical or work-shy individuals, they were understood in the hospital. Here they were fostered and taken care of from morning to night, being, as in Panegrossi's cases, under the personal protection of the Queen of Italy.

Those conditions, undoubtedly valuable to the patients, may, to a certain extent, have interfered with the proper evaluation of the belladonna root extract itself. Therefore I would stress the fact that my patients did not have the advantages of hospitalization, special care, exercises, or improvement of the environment. Most of them were treated in the Neurological Out-Patient-Department of The Mount Sinai Hospital; only a few, in private practice.

The belladonna root extracts were prepared and furnished by Sharp & Dohme of Philadelphia, in accordance with the results of my preceding investigations. Their preparation, "Rabellon," contains 3 mg. of total alkaloids per cc., which consist chiefly of hyoseyamine, atropine, and scopolamine. A synthetic compound, available both in solution and in tablet form, has also been prepared which contains the same alkaloid concentration and proportion as was found by analysis in the clinically most effective extracts of Bulgarian belladonna root. In many cases, this synthetic compound was found to be even more effective than the natural compound. The natural, as well as the synthetic, "Rabellon" is given in very slowly increasing doses before meals or one hour later. I usually start with one drop,<sup>2</sup> three times a day, and increase the dose by one drop daily until a dose from 7 to 10 drops, three times a day, is reached. Subsequently the optimum dose must be determined for each patient individually. It varies from 3 to 25 drops, three times a day, but ranges on the average from 10 to 12 drops, three times a day.

Twenty-six patients have been treated, sixteen of whom were diagnosed as post-encephalitic Parkinsonisms, and ten of the arteriosclerotic or degenerative type. This classification is necessary because the post-encephalitic cases were more benefited by the Bulgarian treatment, although the arteriosclerotic Parkinsonians also showed some improvement.

<sup>2</sup> One cc. of "Rabellon" solution yields about 27 drops. One drop corresponds to about 0.1 mg. of total alkaloids. One "Rabellon" tablet contains 0.5 mg. of total alkaloids, and corresponds to 4-5 drops of the solution. Therefore, one-quarter of a tablet is approximately equivalent to one drop of the solution.



Among sixteen post-encephalitic cases, fourteen showed objective and subjective improvement, in some cases, very marked. A number of this group took up their former employment and lost all symptoms. One of them, a concert-singer, has just gone on his first tour after several years of incapacity and unemployment. Only one patient was unimproved, and one discontinued the treatment after a few days.

Among ten arteriosclerotic and degenerative cases, one discontinued, two were unimproved, and seven showed more or less improvement. One of them felt much better but objectively his condition remained essentially uninfluenced. Another, a depressed grumbler, with signs of senile dementia, was slightly improved objectively but denied any improvement.

In summary, it may be said that the belladonna root extract in Parkinsonism, particularly in the post-encephalitic variety, effects a very quick

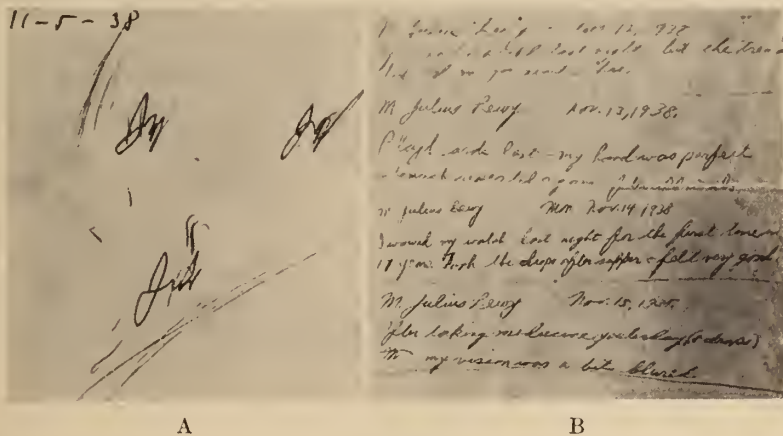


FIG. 1. A. On day of first treatment. B. Seven to ten days after treatment.

response with striking improvement within several days. Most of the patients return after the first week of treatment with such enthusiastic utterances as "I feel 1,000 per cent better," "I am an entirely new person," "That's a wonderful medicine." Most of them say that it is the best medicine they ever had. This initial success and overenthusiasm sometimes is followed by relapses in the succeeding weeks, or the progress slows down or becomes stationary. Naturally, patients expect too much and anticipate a complete cure. Resulting disappointment must be overcome by encouragement. Progressive improvement may continue for months, until the optimum is reached. The drug, of course, must be administered permanently because it brings about only symptomatic improvement. This fact is frequently not grasped by the patients. It is noteworthy that the response to the drug frequently persists even though the treatment is suspended for several days.

The best results are achieved in early cases. But even severe cases of more than fifteen years' duration may occasionally show unexpected improvement. One can not predict which will be benefited and which will not.

Some patients may show intolerance to the drug, mostly on account of individual overdosage. This can be overcome by treating the patient with very slowly increasing doses of the extract. Feverish conditions and hot weather seem to lower the tolerance and should be met by a decrease in dosage. Generally, arteriosclerotic Parkinsonians and old patients show a lower tolerance to the drug.

Improvement is shown mostly in a lessening of muscle rigidity, including amimic, bradykinetic, katatonic, and kataleptic symptoms, in a decrease in muscle spasms, in a fading of disturbances of speech and writing, and in the control of tics and salivation. Samples of handwriting impressively demonstrate the progress (Fig. 1). The hyperkinetic symptoms do not respond as well, but in many cases the tremor is also diminished.

Psychoses due to chronic encephalitis show the least improvement. Less pronounced psychic symptoms, however, such as restlessness, reactive depression or despair respond very favorably to the Bulgarian treatment.

I do not doubt that, in addition, exercises, gymnastics, and institutional care would further improve the results obtained with "Rabellon."

This treatment does not, except in rare cases, bring about a complete cure, or even a complete symptomatic cure. But when neither physician nor patient expects too much, the therapeutic results will be very satisfactory to both in a fairly high percentage of cases. In any event, the Bulgarian treatment seems to be the most effective therapy available at present.

#### SUMMARY

1. The "Bulgarian treatment" of post-encephalitic Parkinsonism consists essentially of the administration of belladonna root extract. Its effect can be supplemented by exercises, psychotherapy, and perhaps a special diet.

2. A standardized belladonna root extract and a synthetic compound in tablet form, "Rabellon," have been prepared.

3. With these preparations, twenty-six Parkinsonians have been treated, with favorable results in most cases. Best results are obtained in post-encephalitic Parkinsonism.

4. This treatment seems to be more effective and less disagreeable or dangerous than the treatment with massive doses of atropine.

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## CLINICAL PATHOLOGICAL CONFERENCES

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, February 23, 1938*

### *Case 1. Carcinoma of the Stomach*

*(From the Medical Service of Dr. George Baehr)*

*History* (Adm. 415680; P.M. 10572). The patient was a 62 year old female admitted to The Mount Sinai Hospital on October 21, 1937. Three months before admission she first noted increasing anorexia, weakness, and considerable loss of weight. During this period she had occasional bouts of syncope, and began to experience attacks of severe upper abdominal pain which arose in the epigastrium and radiated around to the back. These attacks recurred three or four times daily, were occasionally precipitated by eating, lasted about an hour, and were infrequently accompanied by marked dyspnea and palpitation. There was neither nausea nor vomiting. The patient was a widow who had previously borne three children. Her menstrual periods had always been regular until the menopause at the age of 52 years. Since that time there had been no vaginal bleeding or discharge.

*Examination.* The patient was well-developed but appeared chronically ill. The heart sounds were good. The blood pressure was 132 systolic and 80 diastolic. The lungs were clear. A large, hard, nodular mass extending about one finger-breadth below the costal margin was palpable in the epigastrium. Pelvic examination disclosed atrophy of the pelvic organs. There were erythematous discolorations of the skin on the thenar and hypothenar eminences, as well as on the pads of the feet.

The clinical impression was that the patient had a carcinoma of the gastro-intestinal tract with metastases in the liver.

*Laboratory Data.* The blood hemoglobin was 48 per cent; red blood cells, 5,000,000 per cu.mm.; white blood cells, 17,200 per cu.mm.; polymorphonuclear leucocytes, 79 per cent; erythrocyte sedimentation time, 45 minutes. The urine contained three plus albumin and occasional casts. The blood Wassermann reaction was negative. X-ray study of the colon revealed no abnormality. Roentgenogram of the chest showed slight elevation of the right leaf of the diaphragm. The fasting gastric contents showed no free hydrochloric acid. X-ray studies of the upper gastro-intestinal tract could not be undertaken because of the poor condition of the patient.

*Course.* The patient was extremely weak. A liver biopsy specimen obtained by aspiration showed fragments of anaplastic adenocarcinoma. The patient became incoherent and disoriented, and her condition declined rapidly. She died four days after admission.

*Necropsy Findings.* A large saucer-shaped tumor mass was found involving the lesser curvature and posterior surface of the *stomach*, about two and a half centimeters proximal to the pylorus. The tumor measured 3.5 x 3 cm. and was 0.7 cm.



in depth. Its edge was elevated and 0.6 cm. wide. The base of the tumor appeared ulcerated. There were infiltrations of the entire thickness of the stomach wall and involvement of the regional lymph nodes. The *liver* was considerably enlarged and weighed 3,420 gm. Almost the entire liver parenchyma was replaced by large metastatic tumor nodules, about which there were numerous satellite nodules. Only a small portion of liver parenchyma was left intact.

The *right ovary* was enlarged to approximately the size of a tangerine, and was extremely firm in consistency. The surface was nodular. The organ cut with increased difficulty, and presented a strikingly glossy cut surface composed of numerous whitish-gray bands of connective tissue and homogeneous yellow nodular islands.

*Comment: Dr. Klemperer:* The association of an ovarian tumor with a gastric carcinoma immediately suggests the possibility of a Krukenberg tumor (metastatic ovarian tumor). Such tumors, however, are generally bilateral and usually secondary to a scirrhous type of carcinoma.

The unilateral ovarian involvement and the alternating gray-white and yellow zones, unlike the gelatinous appearance characteristic of a Krukenberg tumor, militate against the contention of a metastatic lesion and suggest the possibility of a coincident primary tumor of the ovary.

Histologic sections confirmed the gross impression and disclosed a typical theca cell tumor of the ovary—a purely incidental finding at necropsy.

*Dr. S. Geist:* Theca and granulosa cell tumors represent a group of ovarian neoplasms with distinct biological properties, whose histogenesis is fairly well-established. The theca cell tumor arises from the unused theca cells, forerunners of the ovarian parenchyma, and because of this origin and the properties normally possessed by the theca cells themselves, namely the stimulation of connective tissue formation and the production or storage both of lipid and estrogenic hormones, they possess certain distinctive features. Grossly the theca cell tumor differs from the granulosa cell neoplasm, the former resembling a fibromatous type of tumor. It is hard, white, and the cut surface has a yellowish color, either diffuse or localized to definite larger or smaller nodules separated by connective tissue bands. The connective tissue may be very markedly increased, the fibrils extending between the cells as well as about the large cell islands. Degenerative processes may result in cyst formation. The tumors, while usually not larger than a small orange, may exceed the size of a grapefruit. They are always unilateral. Clinically they occur in the vast majority of cases in women past the menopause. The symptoms are those of any pelvic neoplasm, in addition to those caused by the presence and activity of the estrogenic hormone found in the tumors. The patients usually complain of bleeding, though occasionally in younger women periods of amenorrhea may occur. The breasts are often enlarged and on physical examination the uterus itself is felt to be enlarged and soft. The mucous membrane of the uterus is hyperplastic. These tumors are benign and a conservative operation is all that is required, except in the menopause when hysterectomy and bilateral oophorectomy should be resorted to. Malignant trans-

formation is rare. There are at the present time but two instances of malignant theca cell tumors reported in the literature.

The granulosa cell tumor, which develops from the unused granulosa cells in the parenchyma, differs grossly and morphologically from the theca cell tumor. It is a more succulent, softer, grayer tumor than the thecoma, though occasionally a brownish or slightly yellowish color is present. It too shows degenerative processes which may result in cyst formation. It commonly occurs in two morphological types, the folliculoid and the cylindroid. It does not have the extensive connective tissue growth present in the theca cell tumor nor is the distribution of the connective tissue intercellular as in the theca cell tumor. Fat is scanty and unlike the theca cell tumor rarely occurs in the epithelioid cell islands, but more commonly in the connective tissue. Clinically these tumors also occur in the menopause, but not nearly as frequently as the theca cell tumor. They may even occur in children as young as two years of age. Here, too, aside from the symptoms associated with any pelvic neoplasm, there are signs due to the hormonal activity of the growth. As a result of the estrin stimulation, the patients complain either of bleeding between periods, or of severe bleeding at the periods. At times an intervening period of amenorrhea may exist. The breasts are often enlarged and milk has even been described in the virginal breast, presumably due to the disturbed hormonal action. These tumors likewise are rarely malignant. They may occur bilaterally but unusually are unilateral. In the patient before the menopause conservative operation is all that may be necessary. After the menopause a more radical procedure may be undertaken.

### *Case 2. Putrid Lung Abscess*

*(From the Surgical Service of Dr. Neuhoof)*

*History* (Adm. 413408; P.M. 10650). The patient was a 40-year-old white male who first entered The Mount Sinai Hospital on April 20, 1937. At that time he stated that he had had a cough and yellow sputum for about six months. During the seven weeks before his admission the cough had become worse, and the sputum had become definitely foul. Four days before admission he had developed a mild chill with fever which persisted until the time of his admission.

*Examination.* The patient was emaciated. His oral hygiene was very poor. The teeth were carious. Examination of the lungs disclosed impaired resonance over both apices, and numerous fine, moist râles over the left lower lobe, posteriorly. Expectoration of foul, green-colored sputum was noted. The temperature ranged from 101.6° to 104.4°F.

*Laboratory Findings.* The blood hemoglobin was 76 per cent. The blood Wassermann reaction was negative. Roentgenogram of the chest revealed an area of pneumonia in the left lower lobe, with at least one fluid level.

*Course.* Bronchoscopic examination showed moderately thick foul pus in the bronchus coming from the apical portion of the left lower lobe. Three days after ad-

mission a thoracotomy was performed, and a putrid abscess in the apical portion of the left lower lobe was drained. Following operation, he developed a spill-over infection in the right upper lobe of the lung, with the formation of an acute, putrid abscess in this area. He continued to have fever as high as 103°F. An X-ray of the chest revealed extensive infiltration in the right upper lobe with a well-defined fluid level. Three weeks after the first operation the spill-over abscess was incised and drained. Subsequently, both the cough and sputum became markedly diminished. The patient's condition steadily improved, and he was discharged two months after admission.

*Interval History.* After his discharge the patient continued to expectorate about two ounces of foul sputum a day, although his general condition remained satisfactory. A short time later, however, he was observed in the Chest Follow-Up Clinic, where a roentgenogram revealed increased infiltration about the site of the first operative region in the left lower lobe. Fluoroscopic examination showed an extensive infiltration in the left upper lung field, and a cavity in the right middle lung field. Accordingly the patient was advised to re-enter the hospital.

*Second Admission.* The patient was re-admitted on August 30, 1937. At the time of admission X-ray and bronchoscopic studies revealed the presence of an acute putrid lung abscess which involved the paravertebral branch bronchus of the left upper lobe. It was also noted during the bronchoscopic examination that foul pus was draining from the apical branch of the left lower lobe bronchus, which was the site of the original subacute abscess. The external wound on the right side at the site of the original spill-over abscess, was entirely healed.

Under local anesthesia, the new abscess in the left upper lobe was evacuated and drained.

*Course.* Following operation, the patient's temperature rose to 103°, subsiding to 100-101°F. after five days. At this time his general condition was satisfactory and his expectoration was no longer foul. Additional roentgenographic and bronchoscopic studies disclosed a residual infiltration lateral to the cavity in the left upper lobe. This infiltration extended downward, and was believed to extend across the interlobar fissure to occupy a portion of both the upper and lower lobes. The patient was therefore again operated upon, this time through a posterior axillary approach. A small amount of foul pus was encountered, but no distinct cavity noted. However, in spite of the absence of a distinct cavity, the patient's symptoms and fever persisted. Two weeks after this operation, a cavitation was noted within this area of infiltration, situated in the anterolateral portion of the left upper lobe, well anterior to the previously drained lesion. This cavity was drained. Subsequently, the patient's general condition improved greatly for a period of about one week.

Three weeks after this last procedure, the patient suddenly developed severe pain in the left side of the chest and his temperature, which had previously been normal, now rose to 104°F. Physical examination disclosed signs of fluid.

This was confirmed by X-ray examination which also showed air encapsulated in the anterior portion of the left chest. The patient was again operated upon, and a pyopneumothorax, secondary to a perforation of the putrid lung abscess, was drained. Following this operation, the patient's general condition improved once more. His fever gradually abated, and his temperature fluctuated between 99° and 101°F.

Six weeks after the last operation, however, the patient developed a spiking temperature, which ranged from 99° to 104°F. At the same time a gradually increasing icterus was noted. Upon examination of the abdomen, the inferior edge of the liver was palpated three fingerbreadths below the right costal margin. The liver became progressively larger, extending five fingerbreadths below the costal margin. In addition, the spleen was now palpable two fingerbreadths below the left costal mar-

gin. The urine showed the presence of considerable bile, and urobilin in a dilution of 1:150. It was thought that the patient had developed pulmonary thrombophlebitis, metastatic abscesses in the spleen, and secondary phlebitis of the splenic and the portal veins. Examination of the blood showed the following: urea nitrogen, 10 mg. per 100 cc.; cholesterol, 120 mg. per 100 cc. and a trace of cholesterol ester. The bleeding time was  $5\frac{1}{2}$  minutes; the coagulation time, 13 minutes. The galactose tolerance test was normal. One week after the onset of jaundice the general condition of the patient became rapidly worse, although his temperature had now fallen to 100°F. Ten days after icterus had been first noted and seven weeks after the last operation, the patient died.

*Necropsy Findings.* The pleura over the entire left lung was thickened and shaggy. In the left upper lobe a large biloculated abscess cavity was found. The lower loculation was the larger, and communicated directly with the axillary branch of the left upper lobe bronchus. Two large, gaping, operative wounds opened into this inferior loculation, one on the anterolateral surface, the other on the posterior surface, so that there was formed a tunnel-like excavation through the pulmonary parenchyma. The upper cavity extended superiorly and anteriorly, and ended blindly in the subclavicular portion of the lobe.

Extending from the midportion of the left lower lobe to its apical segment were multiple honey-combed cavities which communicated with each other and with the apical branch of the left lower lobe bronchus.

In the posterior portion of the right upper lobe, just above the interlobar fissure, there was a thick-walled, unilocular cavity, approximately 2.5 by 4.5 centimeters in size. The axillary branch of the right upper lobe bronchus communicated directly with this abscess cavity.

The liver was moderately enlarged, and weighed 2,125 grams. It was very flabby and soft in consistency. The liver had a dirty brownish-yellow color instead of the usual brownish-red. Some areas were golden-yellow. The liver markings were indistinct and in scattered zones completely obscured. Histologically, the liver presented the characteristic picture of acute yellow atrophy. The spleen was moderately enlarged, soft, and its cut surface gray in color. The organ presented the usual findings of the spleen in chronic infection.

*Comment: Dr. Klemperer:* The cause of the icterus must be ascribed to the degenerative changes in the liver. A striking feature of this case is the rapid nature of the disease process.

Wednesday, March 16, 1938

*Osteomyelitis of Femur*  
(From the Orthopedic Service)

*History* (Adm. 414943; P.M. 10591): A 48-year-old white male was admitted to The Mount Sinai Hospital on October 4, 1937, complaining of severe pain in the lower right thigh. Three months before admission a heavy stove had fallen against his right thigh. Since that time he had been having more or less constant pain in the lower portion of the right thigh which had become exaggerated during the month preceding admission. The patient had experienced no fever or chills at any time. On September 27, the patient visited the Orthopedic Clinic of The Mount



Sinai Hospital where an examination revealed excruciating pain in the right knee on internal and external rotation and on flexion of the right knee. A roentgenogram of the lower third of the right femur and the right knee disclosed the presence of a periostitis of the femur with marked thickening of the cortex immediately beneath the lower third of the femur above the condyles. The right knee appeared normal. Roentgenographic studies of the skull, pelvis, and long bones showed no evidence of Paget's disease. Examination of the blood, performed in the Out-Patient Department, revealed a normal content of calcium, phosphorus, and phosphatase. The blood Wassermann reaction was negative.

*Examination:* The patient was well-nourished and well-developed. The lungs were clear. The heart was not enlarged, and the cardiac sounds were good. The blood pressure was 136 systolic and 90 diastolic. The right lower extremity was semi-flexed. There was no limitation of motion at the knee or hip. Some brawny induration was present over the lower third of the right thigh, but the region was not reddened. There was exquisite tenderness over the femoral condyle and lower portion of the femur. The temperature on admission was 100.4°F.

The diagnosis on admission was osteomyelitis of the right femur.

*Laboratory Data.* The urine was normal. The blood hemoglobin was 80 per cent. There were 3,800,000 red blood cells, and 15,000 white blood cells per cubic millimeter (88 per cent polymorphonuclear neutrophils). The blood sedimentation rate was 15 minutes.

*Course.* Two days after admission the patient's temperature rose to 104.4°F. and promptly thereafter, saucerization of the right femur for central bone abscess was performed. At operation, the cortex of the femur showed marked irregularity and deposition of much new bone. There was no evidence of purulent material in the surrounding soft tissue. Drilling the shaft of the femur yielded no pus. However, a wide excision of the lower portion of the shaft caused thick, yellow, purulent material to flow, as if under pressure, from an abscess which was encountered one inch below the center of periosteal swelling. Culture of the purulent material disclosed the presence of *Staphylococcus aureus* A. Immediately following operation the temperature rose to 105.4°, then gradually dropped to 99°F. two days later. A blood culture was negative at this time. The temperature varied between 100 and 103° until nine days after operation when it rose abruptly to 105.4°F. At that time a *revision* of the operative wound was performed. The temperature fell to 100°F. following this procedure, but four days later had once again risen to its previous high level. At this time, because of pain in the right knee, the knee joint was aspirated and thin muco-purulent material obtained; accordingly, the joint was incised and drained. The temperature now became septic in type, and shortly thereafter *Staphylococcus aureus* A was found in the blood. Eight days after this last operative procedure the patient developed tenderness in both elbow joints. These were drained, and the wound in the thigh explored again. *Staphylococcus aureus* A was now cultured from the elbow joints. The white blood cell count at this time showed 15,000 cells per cubic millimeter, of which 68 per cent were polymorphonuclear neutrophils. The temperature remained elevated for several days, and then once again resumed a spiking course, with diurnal variations, occasionally as much as five degrees. In view of the chills and persistent high fever amputation and ligation of the veins of the right leg were considered, but because of the presence of metastatic foci this procedure was deemed inadvisable. The patient was given repeated transfusions, but his condition declined rapidly and he died five and a half weeks after admission.

*Necropsy findings.* The incision on either side of the *right knee* contained purulent material which drained from the knee joint. The anterolateral incision over the lower third of the femur was clean. In the soft tissue encircling this portion, however, there were several intercommunicating pockets which contained purulent material. The lowermost of these communicated with the intercondylar space, and through it with the knee joint, which also contained purulent material. The *periosteum* of the lowest third of the shaft was thickened proximally and destroyed distally where the bone was eroded. At the lowest portion, above the condyles, there was a saucer-shaped excavation two centimeters deep and three centimeters wide. The *cartilages* of the knee joint were eroded and roughened. The entire *femoral and popliteal veins* were occluded by an adherent purulent thrombus which extended into the anterior and posterior tibial veins. The presence of Gram-positive cocci within the thrombus was demonstrated on smear.

The *lungs* showed metastatic abscesses and secondary thrombophlebitis of the pulmonary veins. Purulent infarcts were present in the *spleen* and in both *kidneys*.

*Comment.* Dr. Klemperer: The picture is one of bacteremia. The thrombophlebitis of the pulmonary veins was secondary to metastatic lung abscesses. The duration of the thrombophlebitis in the veins of the leg is difficult to determine from the pathologic findings. This must be deduced clinically.

Dr. Bachr: This is a case of vein infection secondary to the area of trauma in the bone. The initial operative interference was justified, since the temperature of the patient had risen to 104°F. a few hours before operation. However, there is a difference of opinion among surgeons whether acute bone abscesses should be opened immediately or whether a long time interval should elapse before operative interference, in order to permit the infectious process to be walled off, and a sequestrum to separate. I should like to ask Dr. Neuhoef to say something about the advisability of tying off the femoral veins in a case of bacteremia, which is obviously the result of a thrombophlebitis adjacent to the infection of the bone.

Dr. Neuhoef: Suppurative phlebitis derived from an osteomyelitic focus is a lesion which is of interest not only because of its pathological features, but also because of its clinical import. The question of the management of such a phlebitis is certainly a debatable one at the present time. Referring specifically to a *Staphylococcus aureus* phlebitis, it cannot be gainsaid that spontaneous recession can, or does, occur in some cases. To count on such a recession, however, is illogical if there is any surgical method whereby the lesion of the vein can be eradicated. When the great extent of the lesion in the vein is noted at autopsy, as in this case, one's immediate reaction may well be that there is no point in considering eradication of such a widespread phlebitis. The point, however, is that the phlebitis is much more limited at an earlier stage and thus is amenable to at least the possibility of eradication.

There are a number of specimens in the Pathology Department which illustrate the truth of the latter statement. Accordingly, I am of the opinion that at least an exploration of a main venous trunk, known or

assumed to be the site of a suppurative phlebitis, is warranted in many cases in which nothing more than expectant treatment is employed at the present time. Nothing can be lost by such an exploration when properly conducted, and a remedial operation on the vein may be feasible in some of them. I would go so far as to say that even in the presence of metastatic foci, excision of a vein which is the seat of a suppurative phlebitis should be performed if such excision can be carried beyond the limits of the phlebitic process. Indeed, I have seen a few instances in which cure has followed the operation under such circumstances.

In the case presented, operation on the popliteal vein was not seriously considered, as far as I know. Had operation been performed, there would have been no assurance that a phlebitis of this vein would have been encountered. There was a recent instance of osteomyelitis of the tibia, for example, in which an exploration for phlebitis of the posterior tibial and popliteal veins was negative. A phlebitis outside of the infected bone cannot be assumed to exist in all cases of osteomyelitis with maintenance of sepsis. Furthermore, one cannot assume in any given case that a satisfactory outcome will follow excision of the vein even if an excision of the phlebitic vein is carried out. However, it is my opinion that in this case and in similar cases, an exploration of the vein is justified for the reasons which have been advanced.

*Dr. Baehr:* Although it is rare for spontaneous healing to occur in suppurative thrombosis of the veins of the leg, I have seen healing occur in two cases of thrombosis of the periprostatic plexus following drainage of the prostatic abscess. I am inclined to agree with Dr. Neuhof and favor exploration of the veins, draining the infected leg in instances of Staphylococcus bacteremia such as this.

Reported by *Leonard E. Finkelstein, M.D.*

## Henry W. Berg

December 25, 1858—December 22, 1938.

On December 22, 1938 Dr. Henry W. Berg died, aged just three days short of eighty years. His was quite a remarkable career. Born in Austria in 1858, the son of Moritz Berg and Josephine Schiff Berg, he came to this country at the age of five. The family settled in New York City where he attended public school and later graduated with honors from the College of the City of New York in the class of 1878, and from the College of Physicians and Surgeons in 1881. He was a Harsen prize student. During his medical days he was the medical clerk for the eminent neurologist Dr. Seguin, professor of neurology at Columbia. After graduating he assisted the orthopedist, Dr. Newton M. Shaffer, and later became assistant to Dr. Seguin.

Dr. Berg entered general practice and in his early career was interested in orthopedics and neurology, having been made attending neuro-orthopedist at the Orthopedic Hospital where he wrote a paper on *The Etiology of Congenital Club Foot* which won the Alumni Prize at the College of Physicians and Surgeons.

In spite of a rapidly growing practice he found time to write numerous papers, many of them dealing with infectious and contagious diseases, a subject which seems to have fascinated him early in his career and which later was to furnish him with the main theme of his life-work.

In 1893 he was appointed attending physician to the Willard Parker and Riverside Hospitals. He became secretary of the medical board of these institutions in 1894, a position which he held for twenty-eight years.

During the time he was connected with Willard Parker Hospital he saw it grow from a single building to the large efficient institution it is today. His advice and influence there did much to hasten this growth and development. During this time he wrote many articles dealing with contagion—papers on serum therapy for infectious diseases, on antitoxin, chronic laryngeal stenosis following diphtheria, characteristic temperature curves in measles and small-pox, cerebrospinal meningitis and poliomyelitis. He was one of the first intubators for diphtheria in New York City. He was appointed instructor and later clinical professor of contagious diseases at Columbia.

As a teacher of contagious diseases he was unexcelled. His splendid lectures and demonstrations to the physicians and students at Willard Parker Hospital must be remembered by thousands of physicians. He remained on active duty at Willard Parker Hospital till five or six years ago after which he was made consultant.



Dr. Berg was made adjunct physician to The Mount Sinai Hospital in 1899 and associate in 1915. He was also attending physician to the isolation service, and for many years was lecturer to the Training Schools.

In the field of general medicine, his writings included the description of the first case of "Diabète Brouzé" to be reported in this country. He was also one of the first to draw attention to the close relationship between the thyroid and the pancreas in diabetes.

Quite another side of Dr. Berg's career dealt with his relation to civic affairs. He was greatly interested in matters concerning the public schools of New York and was frequently called to the Legislature to give his opinions on economic matters. In 1922 he appeared before the United States Senate on legislation pertaining to immigration. From 1914-1919 he single-handedly fought against compulsory health insurance in New York State. During each of these five years he appeared many times before medical societies and before the legislature of New York State in opposition to compulsory health insurance and helped to defeat every attempt to introduce it into the State.

He was active in the legislature affecting the height of buildings in restricted zones and, as Grover Whalen said of him, he was the first citizen in New York State to be "tax-conscious." He never would accept public office, though he was many times offered the very highest medical-political positions. He was urged by Mayor Mitchell to accept the presidency of the Board of Education.

A-life-long and unusually happy companionship existed between Henry Berg and his brother, Albert, the surgeon—a relationship of mutual devotion and esteem, unique and sustaining.

He was a wide reader and was greatly interested in rare books. His fluency of speech was well-known and he was often called upon as an after-dinner speaker.

He was a member of the Harmonie Club for almost forty years, and of the Grolier Club, the Democratic Club, and the English Bibliographical Society.

In the resolutions passed by the Medical Board of the Willard Parker Hospital the following was said: "The loss to this Medical Board of a colleague possessed of such rare personality is keenly felt today; but its significance will be realized as time passes. Appreciation of the loss of his wisdom and advice will grow in the hearts and minds of us who knew him."

MURRAY H. BASS.

## BOOK REVIEW

*The Cerebrospinal Fluid.* H. HOUSTON MERRITT, M.D., Assistant Professor of Neurology, Harvard Medical School; Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital; and FRANK FREMONT-SMITH, M.D., Formerly Assistant Professor of Neuropathology, Harvard Medical School; formerly Director of the Cerebrospinal Fluid Laboratory, Boston City Hospital. With a Foreword by JAMES B. AYER, M.D. 333 pages with 17 illustrations. Philadelphia and London: W. B. Saunders Company, 1937. Cloth, \$5.00 net.

The largest part of this valuable book consists of a thorough review of the literature, summaries of the authors' own publications, as well as the results of their examinations of some 22,000 samples of cerebrospinal fluid. Under the title of "Cerebrospinal Fluid Syndromes" they discuss the composition of cerebrospinal fluid as found in the several disease entities. Attempts are made to establish quantitative values for changes in cerebrospinal fluid rather than to use descriptions, such as "cells may be normal or increased" or "cells may be moderately or greatly increased." However, in more than a few instances, insufficient statistics still necessitate the use of these relative terms. They also attempt to establish such changes in the cerebrospinal fluid as may occur during the course of each disease. And, finally, they evaluate cerebrospinal fluid findings in differential diagnoses.

The book opens with a brief chapter on the history of our present knowledge of the cerebrospinal fluid. In successive chapters the anatomy of the ventriculo-subarachnoid space and the choroid plexus, the physiology, chemistry, and pathological physiology of the cerebrospinal fluid are considered. The physiology of the cerebrospinal fluid is presented completely, simply, and frankly, without bias. The authors outline both sides of the dialysate-secretory controversy and then state practically their reasons for accepting the former for the time being. The technique for the performance of lumbar and cisternal puncture combined with the technique of routine fluid examination precede the discussion of "syndromes." In this section, the indications for lumbar or cisternal puncture are given, as well as the interpretations of findings.

Lumbar puncture as a means of therapy serves as a topic for another chapter; it is less satisfactory and is filled more with hope than achievement. A section by Dr. von Storch deals with roentgenography of the ventriculo-subarachnoid space. In the concluding chapter by Miss Irvine, an outline of the laboratory methods of choice is presented.

This book, bringing within one compact volume all our knowledge of the cerebrospinal fluid and written in a simple, direct style, serves as an excellent source of information for the clinician and laboratory investigator alike.

J. M. ZUCKER

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Treatment of Obstructed Fallopian Tubes in Sterility by Diathermy and Tubal Insufflation.* M. E. MINTZ. Am. J. Obst. & Gynec. 34: 93, July 1937.

This report is based on the treatment of forty-four cases of tubal obstruction, as determined by tubal insufflation done three times before treatment was started. There were thirty cases of primary sterility and fourteen cases of secondary sterility. Of the forty-four patients treated, patency was reestablished to some degree in twenty-five cases; of these twenty-five women, nine became pregnant and gave birth to normal children. Two patients developed ectopic pregnancies necessitating operations. In fourteen instances no pregnancies have been noted, as yet.

Each patient received diathermy treatments three times a week, the total ranging from fifteen to fifty-nine treatments. Each treatment lasted from thirty to forty-five minutes, using 2,500 to 3,000 milliamperes of current with the abdominal and sacral electrodes. When the abdominal and vaginal electrodes were used, the current employed was only 2,000 to 2,500 milliamperes. The electrodes used were a concave vaginal electrode and, for the abdomen and sacrum, ordinary Cook's malleable metal.

The combined treatment of diathermy and tubal insufflation may produce a favorable result in patients in whom the tubes are the seats of extensive strictures, agglutinations and adhesions which can be overcome by a pressure of approximately 200 mm. of mercury.

Success is less likely when the tubes are organically altered, as in hydrosalpinx. In such instances a pressure of 200 mm. of mercury only rarely produces an artificial opening. Although a pressure greater than 200 mm. of mercury has opened strictured tubes without the use of diathermy, I have not exceeded the maximum of 200 mm. of mercury.

The observation of two cases of ectopic pregnancy in this group is of special interest. Though patency was reestablished in these two cases, the kymographic curve obtained in each during insufflation indicated very weak and shallow contractions at a relatively high pressure level. The curves obtained in the cases of normal pregnancy were rhythmic oscillations at a lower level, as in physiologic tubal patency. Ectopic pregnancy is more likely to develop in tubes which are the seats of adhesions and strictures, where the pressure levels exceed 150 mm. of mercury, as against normal intrauterine pregnancy where the pressure levels are about 100 mm. of mercury or less.

Tubal patency has been reestablished in a small number of cases by repeated tubal insufflations alone and to a lesser extent by diathermy treatments alone. It is very difficult to estimate just how much therapeutic value is to be accorded to the diathermy and how much to the tubal insufflation. There is no doubt that a greater number of successful cases will be obtained by the combined method of tubal insufflation and diathermy, using the vagino-abdominal method.

*Biochemical Studies on Moccasin Venom. I. Some Properties of the Hemorrhagic and Hemolytic Components.* S. M. PECK AND W. MARX. J. Pharmacol. & Exper. Therap. 60: 358, July 1937.

Methods are described for the qualitative and quantitative estimation of the hemorrhagic and for the qualitative assay of the hemolysin of the venom of the water moccasin snake (*Ancistrodon piscivorus*). The effect of pH and heat on these toxic principles is discussed. The hemorrhagic action of moccasin venom is best maintained at pH 6 to 8. With increasing acidity it is diminished. Higher alkalinity also causes deterioration of the hemorrhagin. The hemolysin is most stable at a pH between 4 and 7. There is some deterioration in more acid solutions, complete destruction in alkaline solutions. Both the hemorrhagic and hemolytic principles are completely destroyed at 60°C. The hemolysin is less resistant to heat. It is completely destroyed by exposure to 37°C. for three hours. The effect of shaking a venom solution with chloroform is discussed.

*Tumor of the Brain with Normal Encephalogram.* N. SAVITSKY AND M. B. BENDER. Am. J. Med. Sc. 194: 96, July 1937.

Tumors of the brain, irrespective of their location, nature, size, and rate of growth, may exist for a long time without significant alterations of the ventricular and sub-arachnoid spaces. A series of nine cases of brain tumor with normal aerograms is reported. The locations of the neoplasms were as follows: three were in the parietal lobe, four in the frontal lobe, one in the corpus striatum and temporal lobe, and one in the basal ganglia. The histologic nature of the tumors was as follows: three hemangiomas, five gliomas, and one sarcoma. The duration of the course of the disease up until the time a normal encephalogram was found varied from two months to nineteen years. In four cases, papilledema was found to be present while the ventricular system was normal. In nine cases, the clinical signs were sufficient for localization and diagnosis of tumor. One patient had a normal encephalogram and at autopsy normal ventricles, despite the fact that the tumor was located in the corpus striatum.

Attention is called to the fact that a negative encephalogram does not exclude the diagnosis of a tumor based on clinical grounds. During the earlier stages of a brain tumor, the aerograms may be negative.

*Menstrual Fistula (Tubo-abdominal).* S. WIMPFHEIMER. Am. J. Obst. & Gynec. 34: 146, July 1937.

Menstrual fistula is a term used for a fistula occurring after a laparotomy for uterine or tubal conditions characterized by the periodic discharge of blood, more or less coincident with normal menstruation. An eighteen year old, unmarried patient had previously been operated upon for adnexitis. Both tubes and left ovary were removed. The wound was not drained. With the next five menstrual periods there was a bloody discharge from the scar. The tubo-abdominal fistula was demonstrated by injection of lipiodol into the cervix. At operation a fistulous tract leading to the stump of the left tube was removed with subsequent cure. Specimen revealed tissue spaces lined by foreign body giant cells.

*The Neglected Bulbo-Urethral Glands of Cowper.* A. FIRESTONE. J. Urol. & Cut. Rev., Vol. 41, No. 8, August 1937.

Cowper's glands are discussed from an embryological and anatomical basis. The histology of the gland is reviewed. The various pathological processes affecting these structures are presented and discussed. The importance of these glands in chronic gonorrhea is especially stressed, and the proper procedure for examination is presented. Attention is directed to the need for further studies with reference to the diagnosis of pathological conditions affecting these structures.



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Manuscripts, abstracts of articles, and correspondence relating to the editorial management should be sent to Dr. Joseph H. Globus, Editor of the Journal of The Mount Sinai Hospital, 1 East 100th Street, New York City.

Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

## THE EDWARD GAMALIEL JANEWAY LECTURE II

THE FUNCTION OF THYMONUCLEIC ACID IN LIVING CELLS<sup>1</sup>

EINAR HAMMARSTEN

[Professor of Chemistry of the Karolinska Institutet, Stockholm, Sweden]

The purely chemical properties of thymonucleic acid have been extensively investigated since the time of Kossel's discovery of its basic parts.

P. A. Levene more than any one else has contributed to our present knowledge regarding the *intramolecular* structure of both thymonucleic acid and of the real pentose nucleic acids. His investigations are still in progress, and they will form the basis for our understanding of the functions of nucleic acids in living cells. The *intermolecular* relationships of those acids are also of prime importance for the solution of this very question. In earlier times and even nowadays there is a common belief that nucleic acids combine with proteins by means of some "organic," supposedly ether- or ester linkages (?) that must be split by heating with alkali or digestion with enzymes. In 1920-1928 a pentanucleotide (1, 2, 3) from the pancreas was split by means of a double decomposition with "neutral salt." I. Bang (4; 1918) had studied the influence of sodium chloride on thymus extracts, and by following his directions it was possible to prepare in large amounts the 4-basic salt of thymonucleic acid with sodium by means of a double decomposition at low temperature. In filtration the chlorides or hydrochlorides of proteins remained on the filter as a precipitate while the sodium salt of thymonucleic acid appeared in the water-clear solution. By taking some precautions during the filtration it was possible to obtain sodium salt absolutely protein free (4). Otherwise, a very few small protein particles would pass through the filter causing a slight opacity of the solution. This small amount of denatured protein never influenced the analytical data or the properties of the nucleic acid salt. A far better filtration method was developed by Caspersson for obtaining optically satisfactory solutions (13). For the sake of brevity, I propose the following terminology for thymonucleic acid and its derivatives when it has not been exposed to denaturing influences:

TN for the free thymonucleic acid. TN-Prot. for compounds with proteins (TN-protamin, TN-histon, etc.) and TN-4-b, TN-4-Na for the 4-basic salts with non-specified bases, e.g., sodium, etc. As a nomenclature

<sup>1</sup> Delivered at the Blumenthal Auditorium, the Mount Sinai Hospital, New York City, May 26, 1938.

for the pentose nucleic acids and their compounds the term Pe-N would seem to be appropriate.

The terms TN and Pe-N can not easily be mistaken for other abbreviations and could possibly be useful for the discussions of nucleic acids which will finally be considered especially from the point of view of their *intermolecular* relations, as in the proteins of viruses and bacteriophages, where nucleic acids might temporarily or permanently serve as the combining force because of their high affinity in the polyvalent state (TN or Pe-N). Mononucleotides do not combine with the same force.

The intermolecular properties of TN and Pe-N are determined to a great extent by their intramolecular structure. The dissociation constants of mononucleotides show the expected values, according to Ostwald's law of dilution. The same values for TN-4-Na (4), measured in the usual way, however, can not be considered to represent the properties connected with dissociation, at least not for more than the "first" of the four "constants." This sodium salt dissociates normally according to conductivity measurements. In measurements of osmotic pressure (4, 6), according to Sørensen (14), no appreciable change could be demonstrated even when conditions were very favorable for a membrane-hydrolysis. The measurements were often continued for 4 days with a change of the outside fluid every day. The determinations of the hydrogen ion concentration in the outside fluid were carried out with the accuracy possible in water that is nearly free from traces of electrolytes; but the accuracy of the osmotic pressure measurements was very high ( $\pm 1$  cc. of water). A small percentage of hydrolysis in either direction would have been detected. Other readings (conductivity, freezing point, relative viscosity) have given ample evidence of the fact that TN-4-Na is not easily hydrolyzed, if at all, by dilution or dialysis. Some of the calculated dissociation constants (lower than that of acetic acid) can not be significant. As yet there is no conclusive evidence in that respect concerning Pe-N, a question which ought to be investigated immediately because of its importance in the interaction of proteins and nucleic acids (11, 15).

Before discussing some of the facts concerning these interactions, it will be necessary to describe some of the characteristics of TN. In neutral reaction at approximately 20°C. its lysine-salt is split by dialysis with as little as  $0.5 \times 10^{-3}$  n. NaCl, resulting in the formation of TN-4-Na, a salt with a much higher viscosity. A one per cent solution of this salt in water has a relative viscosity of about 100. Lower figures are due to the presence of electrolytes (e.g., the relative viscosity of 11.15 having been found for a solution of 0.25 gm. TN-4-Na in 100 cc., and falling to 8.5 on the addition of NaCl to make the concentration of  $0.5 \times 10^{-3}$ , a decrease of about 23 per cent). The viscosity, however, is very unstable, solutions often gelatinizing after splitting TN-Prot. by means of neutral salts at room temperature, and even with low concentrations of salt. This might be of interest in the



treatment of virus or bacteriophages with salt, where the formation of gelatinous layers has been reported.

I wish to emphasize the following facts: *the extremely high and unstable viscosity*, the *restricted*: (a) membrane-hydrolysis, (b) Donnan effect, (c) osmotic pressure, the *interactions* with proteins and other basic groups, with gel-formation on double decomposition by neutral salts, and the *threadlike forms* of precipitations (4), *the negative double refraction on mechanical straining of TN-4-Na* (16) or of TN-Prot., the *behavior of TN-4-Na on ultracentrifugation* (12), on *high pressure filtration* (13), the *hydrodynamic data* from determinations of double refraction of flow (19), and *X-ray data* (20).

As yet one cannot form a consistent picture from these facts, but almost all of them indicate that TN is a *restricted* particle. The word "restricted" is used merely to express various types of exceptions to the laws of kinetics. When freedom of movement in the three dimensions of space is totally abolished, a substance is definitely solid, and its only purpose from a biological point of view might be that of structure. A single substance might be restricted in a mono-molecular layer to form a structure, at the same time, however, being more active than it would be in a three-dimensional state, e.g., in solution. The creative mind of Langmuir has made apparent the significance of this connection between the two- and three-dimensional systems, which certainly will become a leading idea in biology. The same constants might be calculated from measurements of a protein film and of a protein solution. They might not be calculated, however, from a film and from a solution of TN-4-Na, because this salt is too restricted and behaves like a stiff rod in solution, refusing to fold up into the spherical shape necessary for the application of the gas laws. The TN and its compounds are restricted to a high degree but are at the same time very active. The whole group of nucleic acids (and perhaps also the acid polysaccharides) have properties of this kind. •

The tremendous viscosity of TN-4-Na could possibly be explained by hydration, but all alkali salts of TN, including protein salts, are always precipitated in the form of long threads, especially in the presence of sodium chloride (4). I could not prove the existence of asymmetrical particles in solution, however, as the cause for the particular form of precipitation.

It was suggested to me by John Runnström that I investigate whether the gelatinized TN-4-Na showed a double refraction after mechanical stretching. He was able to demonstrate a negative double refraction along the axis by stretching the solidified salt and threads of precipitated TN protein (16). These results were of course no proof of a structural viscosity in solution.

Through the courtesy of The Svedberg, who permitted Kai O. Pedersen to investigate the behavior of TN-4-Na in the ultracentrifuge, some very

important facts were revealed. With the permission of Pedersen (12) I give a few examples from the results of his work (October, 1933). The determinations of the sedimentation rate showed a constancy of  $S_{20}$ , at least between  $4 < P_h < 10$ , which would seem to demonstrate that the size of the particles is constant at these different acidities. The measurements of the sedimentation velocity demonstrated the variation of  $S_{20}$  with the concentration "C" of TN-4-Na when this was raised above 1 gm./L.  $C = 0.3$  resulted in  $S_{20} = 10.5 \times 10^{-13}$  but  $C = 5$  gave about half this value which, according to the experience in Upsala, demonstrates the presence of almost thread-like particles. The attainment of sedimentation equilibrium required 2 to 3 weeks with a concentration of TN-4-Na of 1-4 gm./L. in sodium chloride and other solutions of neutral salts (varying between 0.2-1.3 mol.). The substance behaved very abnormally. When the regular calculations from the observations were made, a particle weight resulted which might even be above  $2 \times 10^5$ , likewise, the frictional ratio  $f/f_0 = 2.5$ , the highest asymmetry found as yet. Pedersen states that his results are consistent with an axis quotient of about 1:35 if the asymmetry is presented by a stiff rotation ellipsoid. The apparent diffusion constant calculated from the blurring of the sedimentation curves (in dilute solutions), was about four times that computed from the frictional coefficient. This indicates that the particles do not all have the same size, but this varies around a mean value. The diffusion by the concentration 4 gm./L. was very abnormal and gave quite asymmetrical distribution curves indicating that the particles are restricted. I have only given a few of the values obtained by Pedersen. *They form the first consistent evidence of the true state of thymonucleic acid salts in neutral salt solutions.* I think they are of very great importance.

After studying the viscosity and the double refraction of flow of TN-4-Na, Signer arrived at some conclusions (19). Among them are the statements that this salt had the form of rods with an axis quotient of about 1:300, a molecular weight between  $0.5 \times 10^5$  and  $1 \times 10^6$ . The polarizability was perpendicular to the longitudinal axis with strongly double refracting components arranged in a definite pattern. Apparently the purine and pyrimidine rings lie in planes perpendicular to the longitudinal axis of the molecule. A discussion was deferred, for the present.

The ultracentrifuge revealed the order of magnitude of these particles, which previously was commonly assumed to be about 1500.

The new value of about 200,000 in dilute solutions necessitates the review of some observations from the year 1924 (4) on osmotic pressure and the membrane effect on the distribution of dialyzable electrolytes. The latter measurements in the system containing TN-4-Na + NaCl and using a collodion membrane resulted in the applicability of Donnan's law of equilibrium:

$$\text{Cl}_i/(\text{Cl}_i + 0.78 \cdot \text{Na}/4) = \text{Cl}_o^2 \pm 14.4 \text{ per cent.}$$

where  $Cl_i$  is the concentration of sodium chloride in the solution containing TN-4-Na,  $Cl_o$  that in the outside solution and Na the concentration of sodium in TN-4-Na. It was concluded at that time (4, p. 19) that the sodium ions in TN-4-Na had a degree of activity, according to Donnan's law, corresponding to about one-quarter of the activity that would have been found in complete dissociation. An attempt was made to determine the value  $\frac{\mu_v}{\mu_\infty} = \alpha$ , and this was found to amount to the same as that of other sodium salts, i.e., about 0.8 in the concentrations used. In 14 rather accurate determinations of the osmotic pressure, given in Table I, the quotient between the pressure found ( $P_f$ ) and the one calculated for only one quarter of the sodium content in the TN-4-Na =  $P_c$  was 0.80.

TABLE I  
*Osmotic pressure of TN-4-Na in centimeters Hg  $\times 13.55$*

$P_f$	$P_c$	$P_f/P_c$
6.5	7.9	0.82
13.0	15.1	0.86
25.0	30.9	0.81
31.0	38.2	0.81
47.7	58.6	0.81
69.0	86.4	0.80
82.5	103.6	0.80
83.1	104.0	0.80
83.5	106.0	0.79
82.0	99.1	0.83
85.6	109.4	0.78
85.8	109.0	0.79
80.5	109.0	0.79
173.2	217.9	0.79
Average .....		0.80

The determinations of the molecular weight in diluted solution (by Pedersen in 1933) made it necessary to disregard the molecular weight of the TN-particles (table I). The smaller ions had about 0.2–(0.25) of the expected thermodynamic activity. This phenomenon has been called a volume effect. Similar effects have been observed in osmotic measurements, with proteins and other electrolytes of high molecular weight (4, 6, 7, 8, 9). This effect may possibly be related to the presence of oblong, stiff structures in solutions of TN-b. The effect is diminished by raising the molecular volume of the smaller ions. Nothing is known, however, in this respect about TN-Prot. In this connection the calculation of Linderström-Lang in 1926 (5) should be mentioned. One of his conclusions founded upon Gibbs' calculations for the stability of one-phase systems was that the activity of the large ion must be a diminishing function of the

concentration. It was also concluded that the large ions must associate to a very high degree. The formation of "micellae" was suggested as a possible explanation. It was stated, however, that this word could not be used in the classical sense. *These results, as well as Pedersen's, will probably be of great importance in the investigation of polynucleotides and of other electrolytes with a high particle weight.*

Thanks to the high degree of restriction combined with a still higher activity, TN is a uniting, structure-forming force in the living cells, capable of directing the ion- and water distribution. To some extent similar capacities probably are characteristic for Pe-N, especially for Pe-N-Prot.

The interaction of TN and proteins have been studied but superficially. In model experiments TN forms various salts with different sorts of proteins (15). All of them, and the naturally occurring TN- and Pe-N-Prot. in thymus, sperm and pancreas (1, 2, 3) respectively, could be quantitatively split by the action of neutral salts at a low temperature provided that one of the constituents was removed from the system. The viscosity was raised by these reactions indicating the formation of  $\text{TN-Na}_n$  ((4) Fig. 18) through the action of which the structure easily may be changed to a gel. The amount of protein combining with TN is influenced by: (1) the hydrogen ion concentration, (2) the amount of neutral salt, (3) the relative amounts of protein and TN, (4) the nature of the protein (11). There are indications of other influences, such as the nature of the salts and the presence of lipins, but very little is known about that. Basic proteins can form insoluble salts at neutral reaction but also soluble ones (4) while salts with acid proteins are formed as insoluble salts first at a pH which is lower than the isoelectric reaction of the protein. That neutral compounds can be formed with acid proteins is very probable but the investigations regarding this question are not yet ready for publication. If insoluble salts of an acid protein and TN are dialyzed against a solution of sodium chloride, TN-Prot. precipitated at pH 2-3 or lower will dissolve, and the pH will rise close to the isoelectrical reaction of the protein (11, p. 191). By the splitting process protein hydrochlorides must have been formed, and by membrane hydrolysis a *neutralization by neutral salts is brought about.*

This would not have been effected, if the newly formed  $\text{TN-4-Na}$  had been hydrolyzed in the same degree, which is not the case as stated before. It is not yet known if  $\text{Pe-N-Na}$  would also resist hydrolysis. Of course it is necessary that one of the components formed during a double decomposition be removed in order to complete the reaction. The conditions must be very favorable to permit a quantitative splitting of a salt into nucleic acid and protein merely by dissolving it in salt solution and saturating the solution with salt. If such a procedure is carried out as a fractionation with salt, the probability of getting more than a very small percentage of the original nucleic acid as protein-free nucleic acid would seem to be very small, if the nucleic acid is present in the form of a polynucleotide. The



mononucleotides are quite another proposition, as their affinity towards proteins is so small compared with that of a polynucleotide as to be of a different order of magnitude. In the former example, the polynucleotide would be found in all fractions if the nucleic acid or the protein were not removed at the same velocity as its formation. I have had many profitable discussions on this question with Dr. Michael Heidelberger, and it will be of great interest to investigate whether solutions of "naturally" occurring "nucleoproteins" are split into protein acid salt and nucleic acid salts with the kations, in all cases where Pe-N is concerned.

The compounds of the latter might be less restricted judging from the tremendous difference in viscosity between TN-4-Na and Pe-N-b, but it is by no means certain that the structural capacities and the viscosity are necessarily related. In any event, all polynucleotides have the remarkable activity in the presence of proteins and even amino-acids consistent with the polynucleotides' character of heavily restricted, strongly dissociating electrolytes. In these days of revived appreciation of the primary biological importance of the nucleic acids, it will be well to keep in mind that the reversible formation of the manifold compounds made up of proteins and nucleic acids is favored by hydrogen ions and by other very active kations (some dyestuffs, lanthanum ions and even twovalent ions) and also an excess of protein, especially if it is more basic than acid. This reaction is impeded by neutral salts and an excess of nucleic acid. The precipitations are always thread-like, all compounds being contractile and showing a negative double refraction on mechanical straining. Very small amounts of nucleic acids can associate large amounts of proteins into big particles (rather than molecules). Nucleic acid, especially when in excess, effectively prohibits the denaturing of the protein part (4, 11). The formation of precipitates may easily be caused in the presence of basic proteins, or also through the combined effect of carbon dioxide and dialysis. The action of salt in small concentrations may intensify the restrictedness of solutions so as to form a gel. TN-4-Na at least does not behave according to the gas laws (contrary to mononucleotides) but has combining structure-building capacities with an activity of determining influence upon ion- and water-distribution in cells.

A recent X-ray study by W. T. Astbury and Florence O. Bell (20) on TN-4-Na has not only amply confirmed earlier observations on the restrictedness of this substance by measurements in an almost dry state but also revealed constant periods along the fiber axis. One of them is 3.34 Å.U. i.e., the same as that in an extended polypeptide chain. The occurrence of this period is very interesting in connection with earlier observations by Pedersen and Signer (l. c.) and might correspond to the distances between the very active, acid groups located in the molecules of phosphoric acid in TN. The degree of restrictedness of these groups can be expressed by a number about 0.2 times the maximal value, but this value is applicable

only to small ions (the volume effect). This effect demonstrates in fact that a much greater number of the acid groups in TN, perhaps all of them, could be linked to protein molecules of equal or different sizes. One particle of TN with a weight of up to  $10^6$  could then possibly carry "protein particles" to the highest number calculated by Astbury, of some 2000. Of course it is too early to speculate too much on Astbury's interesting results, but the fact of the uniting force of TN was ascertained long ago, and such a restricted uniting force could be helpful in trying to explain the properties of viruses and bacteriophages. I am by no means alone in considering as important the function of nucleic acids for this "synthesis" or uniting, considerations backed by the fact that viruses and phages are reported from many sides to contain nucleic acids. It is easy to conjecture an active particle where specific proteins are united by nucleic acid to form what ought to be called a *living particle* instead of a living molecule. The last word is reserved by the chemists and the quite unnecessary use of it in dealing with "self-activating" particles seems only to spread confusion.

I feel that it is appropriate in this connection to call attention to the rather obvious fact that other restricted electrolytes in living cells may play a similar rôle. Acid polysaccharides are linked with proteins, and some of these compounds react with neutral salts much in the same way as salts between proteins and nucleic acids. I cannot resist the temptation to remark that the uniting or "synthesizing" substances of the kind discussed now could possibly be removed after having fulfilled their purpose of "bringing together" without impeding the activity they helped to organize. This view would place nucleic acids in one respect at least on the level with enzymes, some related substances, the pyridine nucleotides, actually being enzymes. On the other hand the rôle of nucleic acids could be of permanent importance to this activity.

The work, "Molecular sizes and cataphoretic properties of tuberculin protein molecules" by Seibert, Pedersen and Tiselius (24) gives some indications concerning a possible rôle of nucleic acid. A protein fraction with high potency and low molecular weight at some stage of the preparation was linked with nucleic acid but no protein of this low size occurred in the original culture medium.

A direct application of the properties of TN here described to functions in living cells was made at an early stage in my work. Much time was spent with tissue culture and micro-manipulation to obtain some method for tracing the varying structure which must necessarily be built by the differently restricted salts of TN, especially those with proteins. It must be remembered that there was no consistent evidence at hand to demonstrate even the presence of protein in cell-nuclei or chromosomes. The presence of nucleic acid was proved for some cells, and the results from cytological staining were fairly conclusive in some respects. Schiff's reaction as applied by Feulgen is not always specific, however. The formation of

practically insoluble salts of TN and lanthanum ions seemed to be more promising, the general idea being to precipitate nucleic acid or protein separately and dissolve the unprecipitated compound, thus revealing the structure (the former position) of the latter in cells. I will only mention here that T. Teorell and I succeeded in demonstrating the presence of protein in cell-nuclei in mitosis and its absence in the nuclei at another stage by using lanthanum salts, sulfosalicylic acid and dyestuffs. The material (red blood corpuscles from Triton) was not easy to handle, and so I tried model experiments. Having developed some methods for precipitating a protein-free nucleic acid with lanthanum ions in the presence of malonic acid and of protein free from nucleic acid, by using zinc ions in the presence of formalin and sodium chloride, my collaborators, H. Hammarsten and T. Caspersson, and I investigated the possibilities of dissolving the proteins with protein-splitting enzymes, keeping the nucleic acid in a precipitated form by raising the concentration of lanthanum ions during the digestion. If improved, I think these methods may be useful, as it was possible by the application of enzymatic digestion or malonic acid in the presence of lanthanum ions to locate conclusively for the first time both the protein and the absorbing part of nucleic acids, using Koehler's equipment and the experimentally found appropriate wave-length of about 2600 Å.U. (15).

When these combined methods were applied to the chromosomes of the salivary glands of *Drosophila* larvae, the characteristic banded structure of such chromosomes was shown to be due to an alternation of protein and nucleic acid (17, 18).

In the continuation of this work Caspersson has developed methods (23) enabling him to measure quantitatively the absorbing parts in nucleic acid (pyrimidine rings) in different locations of one single cell and in different parts of one chromosome. I think that Caspersson by his methods has made possible a new approach in cellular physiology. It has never before been possible to measure accurately not only the amounts but also the positions of various constituents in one single cell. As a matter of course there is much work ahead, but from a principal point of view I can see no reason why the amounts, positions and even facts concerning the formation of every constituent of living cells should not be determined quantitatively by following Caspersson's happy combination of modern devices for using light and electrical energy without destroying or impeding the processes in living cells.

This is not the time to enter upon a description of these methods which Caspersson has worked out. It was a lucky thing that J. Schultz of the Carnegie Institute in Pasadena, working on problems concerning translocation involving heterochromatic regions in the chromosomes of *Drosophila* larvae, saw the possibility for an application of Caspersson's methods to his own observations. I can only give a brief account of some results

of great importance (21, 22). As a result of a translocation the heterochromatic region of the 4th chromosome is juxtaposed to a portion of the X chromosome. Schultz had previously observed a darker staining of the bands in this haploid X as compared to its homolog. The measurement demonstrated clearly and quantitatively the higher content of pyrimidine rings in the bands of this haploid X. The difference in question is greatest in the vicinity of the heterochromatic region of chromosome 4. The introduction of a Y-chromosome (heterochromatin) into females showing translocation involving heterochromatic regions will diminish this difference. Oocytes from such females have a higher content of "nucleic acid" (rather, matter with an absorption maximum at 2600 Å.U.) than oocytes from females without the Y-chromosome. The introduction of a Y-chromosome into the race concerned here will also abolish or diminish the

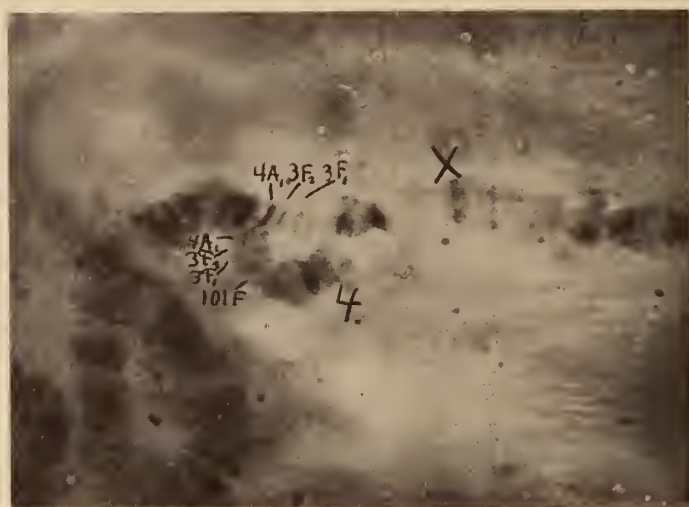


FIG. 1. 2600 Å.

frequency of abnormalities in the genetic constitution. The results seem to be highly in favor of the conclusion that nucleic acid or related substances influence the constitution of the genes. These are, as I have said, only a few of the results of Caspersson's and Schultz' fundamental work; it has already progressed far enough to indicate what far-reaching genetic effects may be produced by changes in the nucleic acid metabolism of the cell. Basic to the understanding of such work is the analysis of the intermolecular properties of the nucleic acids by Pedersen, Signer, Astbury and others.

For this reason I have tried to give some of the background of the latest reported results. In that way I hope that the latter will arouse the interest they deserve and that attention will be drawn to the great expect-



tations of further developments regarding the intermolecular functions of nucleic acids.

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## PSYCHIC FACTORS IN RECURRENT GRAVES' DISEASE

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The rôle of psychic trauma in precipitating the Graves' syndrome has been long recognized. The more dramatic, if less common, form is characterized by the rapid, and at times fulminating, evolution of the disease following a specific emotional cataclysm. The impressionable witness to a scene of horror, such as violent death, is singularly susceptible. Instances of tremor, tachycardia, and exophthalmos appearing within twenty-four hours after a profoundly shocking experience have been recorded. It cannot be gainsaid that the impact with a peculiarly intolerable situation may be merely the fuse that sets off long-smouldering emotional dynamite, thus serving to accelerate rather than to initiate the clinical picture.

The more common mechanism, however, is the slow, almost imperceptible development of the disease after a long succession of subminimal traumata extending over months and sometimes years. Victims of prolonged privation and reversals, marital and familial maladjustments, sexual frustrations, and countless other conflicts present the essential *anlage* for Graves' disease. The quasi-intellectual who resents "degrading" labor, and the ambitious youth who is constantly thwarted by economic inadequacy are random examples.

Adequate prophylaxis in Graves' disease presents almost insurmountable obstacles. Born and bred of the individual's conflict with an inelastic environment, which is closely interwoven with our entire socio-economic structure, the futility of its correction is apparent. In the post-thyroidectomy phase, on the other hand, there is a generally neglected field where prevention is vitally needed. The sense of security manifested by most surgeons fortified with the belief that a permanent cure will have been effected in Graves' disease after the removal of 80 to 90 per cent of the hyperplastic thyroid tissue is hardly justified by the results of a critical follow-up. Thyroidectomy, it is self-evident, does not materially alter the so-called "Graves' personality." At best, the hypermetabolism of hyperthyroidism is controlled with a subsidence of the associated phenomena. The underlying psychic pattern, except in rare instances of myxedema, remains a *locus minoris*, peculiarly keyed to a maximum response to minimal stimuli. The belief that thyroidectomy presents an opportunity for arresting the disease which subsequent intelligent control

may ultimately cure, is in distinct variance with the conception that operation terminates the disease.

#### CASE REPORT

*History* (L. Z., Adm. 361399). A 32 year old married woman was admitted on January 10, 1934, complaining of nervousness, emotional instability, palpitation, and enlargement of the neck of three years' duration. Her personal history presented many interesting features and will be given in some detail. She was born in a small Polish town, the youngest of ten children. Her father was the prosperous owner of a large lumber mill and the children had had private tutors, numerous luxuries, and prolonged holidays at a variety of European spas. The most affluent family in the community, they were inclined to look upon their less fortunate neighbors with mild contempt. She was pampered by her elders and encouraged in her talents for poetry and music. Her imaginativeness led to constant day-dreaming, and her writing assumed a mystic quality. She can recall no experience that marred her happy childhood. At the age of twelve her idyllic existence was shattered by the advent of the World War. Her father's business was ruined, the town was a shambles, three of her brothers were killed and she was an eye-witness to numerous atrocities. For four years she lived with the remnants of her family in semi-starvation and terror. Crushed by suffering, her poetry, now more profuse, took a melancholy turn with futility as the dominant theme. She was sixteen when the war ended and the period of readjustment did little to improve her lot. Working as a waitress, she saved enough to come to America where she was employed in a tie factory for three years. At nineteen she was married to one of her shopmates, a native of her home town, whom she can recall as socially inferior and living on 'the other side of the tracks'. Considerations such as love and respect were ignored when she saw an opportunity for escape from the drudgery of the factory. Her relative ease was soon dissipated by the birth of three children in four years and the increasing cares of the household. Her husband's devotion never quite compensated for the replacement of her girlhood dreams by the realities of poverty and monotony. She became increasingly resentful of her plight, but found an escape in writing. Shortly after the birth of her fifth child, three years ago, nervousness became marked, heat intolerance and bulimia appeared, palpitation was constant, and she lost much weight. Following a brief stay in the country she improved considerably until the death of a relative at the hands of gangsters, at which time all of her symptoms returned. Exophthalmos and neck enlargement appeared and the basal metabolic rate was plus 48 per cent. With large doses of Lugol's solution, her signs diminished and the metabolic rate fell to plus 3 per cent. There was a rapid exacerbation of her symptoms two months before her admission to the hospital, accompanied by severe diarrhea.

*Examination.* The patient was a hyperkinetic woman of 32, of active intelligence. There was prominence of the eyes, more marked on the left, and a distinct coarse tremor of the fingers. The thyroid gland was uniformly enlarged and firm. The pulse rate was 112 beats a minute and the blood pressure 132 systolic and 56 diastolic. There was a pronounced skin tache and the deep tendon reflexes were markedly exaggerated. Aside from overactivity, the heart was normal. The hemoglobin was 67 per cent; leukocytes, 8,000 with a normal differential count. The admission basal metabolic rate was plus 61 per cent.

*Course.* Her pre-operative preparation was marked by fits of crying and depression and several quarrels with her neighbors with subsequent agitation. There was no fall in the metabolic rate for the first week. Medication with Lugol's solution, however, was immediately effective; she became calm and the basal metabolic rate fell to plus 24 per cent within eight days.

*Operation.* On February 2, a subtotal thyroidectomy was performed by Dr. Lewisohn under gas-oxygen anesthesia. Both lobes and most of the isthmus were resected, leaving stumps approximating less than 10 per cent of the total thyroid tissue. She bore the procedure without mishap and the pulse did not exceed 90 beats a minute at any time. The pathologic report by Dr. Klemperer follows: "Specimen consists of a subtotal thyroidectomy. Both lobes and the isthmus were removed. The amount of tissue aggregates a mass 5 cm. in diameter. The lobes are well encapsulated; the tissue is uniform in character; on section it is fleshy in appearance and contains a small amount of colloid. Microscopic study revealed a hyperplastic thyroid in the colloid phase."

On the third postoperative day, paroxysms of auricular fibrillation with ventricular rates of 160 or more appeared; these episodes were frequently followed by periods of paroxysmal tachycardia, auricular in origin. During the arrhythmia she became extremely apprehensive and at times hysterical. Normal sinus rhythm, rate 80, was spontaneously restored at the end of three days. Her improvement was rapid and she was discharged three weeks after operation distinctly improved, with a basal metabolic rate of plus 10 per cent.

*Subsequent Course.* The patient was seen in the Thyroid Follow-Up Clinic in March and September 1934 and was found to be in excellent condition. She had gained twelve pounds in weight, the pulse was slow, the tremor had disappeared and she appeared emotionally stable. She failed to keep her subsequent appointments, but wrote on January 26, 1936 that "she was feeling fine". She was not seen again until November 4, 1937 when she complained of palpitation, tremor, increasing nervousness, heat intolerance, and weight loss. She again presented the picture of a florid Graves' disease, and the basal metabolic rate was plus 58 per cent.

*Second Admission* (November 24, 1937). She stated that she had been fairly well until a year previously when she noted an increase in appetite, fluctuating emotional instability, moderate tremor and palpitation, and gradual weight loss. These symptoms appeared shortly after her husband lost his job and was forced to go on relief. Her literary leanings had by no means been neglected during this period, and she had been at work on a novel which she happily named "A Saga of Death". Similar morbid trends were noted in incidental poetry. Of primary importance as a specific recurring trauma was her complete emotional projection into the Spanish conflict with its numerous implications; this soon reached obsessional proportions so that she could think of nothing else. During the siege of Madrid she was unable to sleep and was keyed to a pitch of constant excitement. Developments in totalitarian countries were only second in importance as irritants. On examination the exophthalmos was again pronounced, tremor was coarse, and the thyroid uniformly enlarged; crying spells and agitation were frequent. With Lugolization the symptoms promptly diminished and the basal metabolic rate fell to plus 14 per cent, when a subtotal thyroidectomy was performed by Dr. Garlock on December 13th. A considerable mass of thyroid tissue was found on each side of the trachea, the mass on each side approximating the size of a plum. After resection of the recurrent tissue, small portions were left posteriorly. There was a transient right recurrent laryngeal paralysis but the patient's postoperative course was otherwise uneventful. The specimen, as described by Dr. Klemperer, "consists of a partial thyroidectomy. Both lobes have been partially removed. They are somewhat ovoid in shape, measuring 4 cm. in the long diameter, 2 cm. in the short diameter. The tissue is encapsulated except at the line of resection. On section the thyroid tissue is uniform in character. The lobular structure can easily be made out. It contains a fair amount of colloid. Both lobes are similar in character. Microscopic section revealed hyperplastic thyroid as seen in Graves' disease in the colloid phase". Her recovery from operation was prompt and within a few days she lost all of her in-



stability, palpitation, and tremor. A recognition of the vital rôle played by her emotional trends and fixations in precipitating recurrences, suggested closer supervision and follow-up. Frequent consultations were held with the patient and definite progress was made in developing a more roseate point of view. When last seen (November 10, 1938) she was asymptomatic.

#### COMMENT

There is growing recognition of the fact that thyroidectomy does not alter the fundamental Graves' personality. The removal of most of the hyperplastic gland permits the individual to make an adjustment impossible in the presence of an elevated metabolism. The residual thyroid tissue, no matter how small it may be, acts as a "shock organ" and may become acutely responsive to a succession of psychic traumata. Intelligent control for many years after operation should materially lower the number of relapses. Constant vigilance is essential in protecting the patient from those situations and conflicts which tend to reactivate the underlying, if arrested, disease.

#### CONCLUSION

The prevention of recurrences in Graves' disease can be effectively controlled to a considerable degree by intelligent supervision and psychotherapy for a prolonged period following thyroidectomy.

## ROENTGENKYMOGRAPHY IN THE DIAGNOSIS OF MYOCARDIAL INFARCT

WITH NORMAL ELECTROCARDIOGRAMS

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The value of roentgenkymography in the diagnosis and study of myocardial infarct has not yet been established. It may be stated at this time that the kymogram yields definite evidence of myocardial damage in most cases of coronary occlusion. From the diagnostic point of view, ordinarily, little is added, since serial electrocardiograms are usually positive. However, the following two cases illustrate the fact that the kymogram may be positive even when serial electrocardiograms are negative. The value of the test under these circumstances is evident.

### CASE REPORTS

*Case 1. History* (Adm. 432558). A male painter, 55 years old, was admitted to the Out-Patient Department in November, 1937. He complained of indigestion, sticky pains all over the body, and headache. The next day he was feverish, coughed, and felt that he had caught cold. He remained in bed for two weeks. On the evening of December 20, 1937, while lying in bed, he suffered an attack of precordial oppression which radiated to the left shoulder and arm. At the same time he had a cold sweat. The attack lasted all night; it was followed by another attack the next night. The patient was then admitted to the hospital.

*Examination.* The physical examination was essentially normal, except for a few coarse râles at the left base. The blood pressure was 175 systolic and 110 diastolic. Hypertensive changes were found in the fundi. The man was obese; his weight was 170 pounds.

Psychiatric investigation revealed a marked narcissistic element in the patient's illness and an unconscious exploitation of his symptoms. He was tremendously concerned with the details of his symptoms and resented any inference that he was not very sick. When he was told he was getting well he had temper tantrums. A definite anxiety neurosis was present which, it was thought, aggravated the anginal syndrome.

*Laboratory Data.* Serial electrocardiograms were normal. Vital capacity was 2500 cc., circulation studies were normal, white and red blood cell counts and sedimentation rate were normal. The blood pressure dropped to 110 systolic and 70 diastolic and then rose again to 130 systolic and 90 diastolic.

Roentgenkymograms made on December 24, 1937, January 6th, and January 18th, 1938 all showed definite lateral movement in systole over the lower left contour, seen in both sagittal and left oblique views. These findings indicated the presence of a myocardial infarct.

*Course.* At the time of this admission, the clinical diagnosis was angina pectoris and essential hypertension.

While in the hospital the patient continued to have attacks of precordial pain which were relieved by the hypodermic injection of sterile saline.

After discharge from the hospital the patient continued to complain of precordial pain, weakness, insomnia, and nervousness. In July, 1938, the precordial pain increased; it was relieved by nitroglycerin, while the neurotic symptoms became more evident. The blood pressure was found to be increased to 210 systolic and 130 diastolic. In November, 1938 the patient complained of choking sensations and cough after each attack of precordial pain. The heart was slightly enlarged. There was a systolic murmur heard at the apex. The exercise tolerance test was abnormal. Blood pressure was 174 systolic and 124 diastolic. Vital capacity was 2600 cc. The

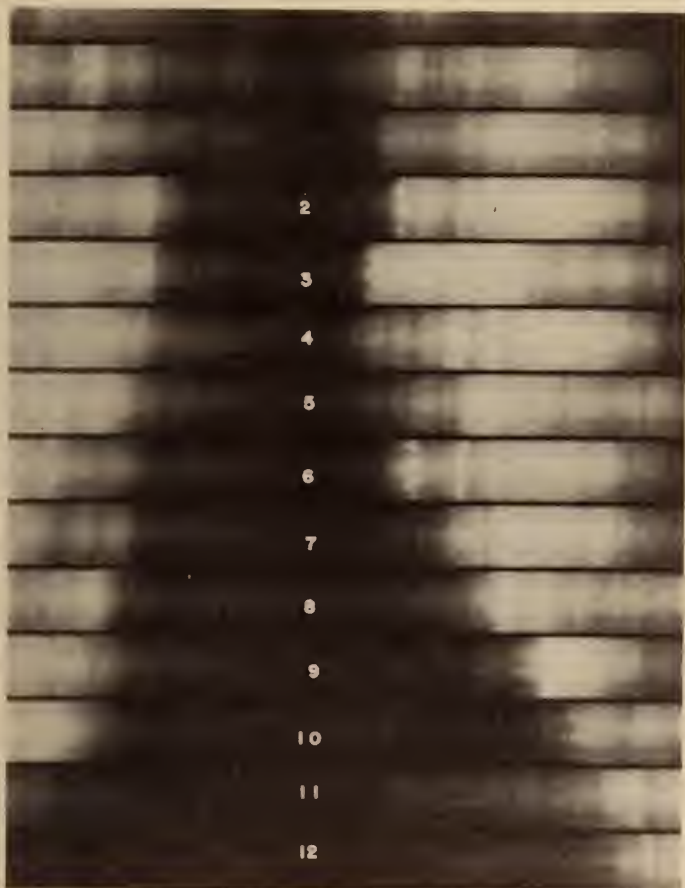


FIG. 1 (Case 1). Roentgenkymogram shows distinct lateral systolic movement over the left ventricular contour, well-defined in intervals #9 and #10.

electrocardiogram remained normal. The roentgenkymogram still revealed evidence of myocardial infarction.

The patient also had heartburn and epigastric pain, especially at night. Gastro-intestinal series, repeated several times subsequent to 1932, failed to show evidence of an ulcer but did demonstrate the presence of a diaphragmatic hernia.

*Comment.* The negative electrocardiograms and the presence of a definite anxiety neurosis made the clinical diagnosis of anginal syndrome and

essential hypertension more likely than that of coronary artery occlusion. The case emphasizes the following facts:

- (1) Anxiety often appears in individuals with organic disease.
- (2) Negative serial electrocardiograms do not exclude coronary occlusion.
- (3) Cases of anginal syndrome should be investigated by roentgenkymography before the diagnosis of coronary occlusion is excluded.

*Case 2. History* (O. P. D. Adm. 38-9626). A male painter, age 57 years, was admitted to the Out-Patient Department on December 17, 1938. For seven to eight



FIG. 2 (Case 2). Roentgenkymogram shows localized diminution in pulsation at mid-left ventricular contour and lateral systolic movement at the apex.

months the patient had complained of attacks of pressing pain in the xiphoid area radiating through to the back. The pain would start suddenly, last five to eight minutes, and then disappear abruptly. At the beginning, the attacks occurred once a month but later they became more frequent, so that at the time of admission they occurred several times a week. When the oppression was severe the patient found it difficult to breathe. The attacks had no relation to meals or any significant gastro-intestinal disturbance.

*Examination.* Aside from pulmonary emphysema with squeaks and rhonchi throughout the lungs, there were no abnormalities. The heart was not increased in size to percussion. The heart sounds were somewhat diminished at the base. On



January 25, 1939 a tender mass believed to be a large gallbladder was palpable in the right upper part of the abdomen.

*Laboratory Data.* The blood pressure was 116 systolic and 74 diastolic. Electrocardiogram was normal. Exercise tolerance test was within normal limits. Graham test was normal.

Roentgenkymogram on January 25, 1939 revealed definite lateral movement in systole in sagittal and left oblique views, indicating a myocardial infarct.

*Comment.* One observer made the following clinical note prior to roentgenkymography, "despite the normal electrocardiogram, this patient probably has coronary sclerosis as the cause of the angina. The story is not that of gall bladder disease despite the palpable gall bladder."

#### SUMMARY

Two cases are presented in which the history was suggestive of coronary occlusion. Normal electrocardiograms were taken. Definite systolic distention of the left ventricle was revealed by roentgenkymography. Although our information regarding roentgenkymography is still without sufficient postmortem corroboration, there are few conditions other than myocardial infarct which would permit systolic ventricular distention. Scott et al. (1) reported the finding in a case of myocardial tumor. The explanation of the absence of electrocardiographic changes is better left until postmortem studies are available.

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## ANGINA PECTORIS OF PSYCHOGENIC ORIGIN

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In this report attention is drawn to the observation that an anginal syndrome, generally considered typical of coronary artery disease, may occur in the absence of such disease, on an entirely psychogenic basis. In the case reported here, it was attributed at first to organic coronary artery disease, but was later shown to be entirely psychogenic in origin. A number of similar cases have been observed by us.

Heberden's (1) classic description of angina pectoris has, in the main, held to this day. He described "a painful sensation in the heart while walking and more particularly while walking soon after eating. The os sterni is usually pointed to as the seat of the malady." It is generally believed that such an anginal syndrome is caused by coronary artery disease and can be differentiated from a functional syndrome by the type of pain. In the organic type, the pain is nearly always substernal and occurs as a rule after exertion, meals, or excitement, whereas in the functional type, the pain is usually over the precordium or nipple, often lasts longer, and is not related to effort. In the main, this differentiation holds true but, as is demonstrated by this case, angina of psychogenic origin may also be substernal and come on with exertion.

### CASE REPORT

*History* (J. S., Adm. 34-19506). A Polish-born Jewish cloak-maker, 29 years of age, was admitted to the Angina Pectoris Clinic in 1934 for precordial pain of three months' duration. Three months previously he had been seized with agonizing substernal pain radiating to the left arm. A private physician made a diagnosis of coronary artery occlusion. Since then he had had frequent attacks of precordial pain radiating to the left shoulder and back. The attacks were usually associated with exertion or excitement. He was unable to work or to walk more than two blocks; on two occasions he had been seized with syncope and pain while walking in the street and an ambulance had to be summoned. On one of these occasions he was taken to a city hospital because of the suspicion of coronary occlusion but after a short period of observation was discharged because of the impression that he was not suffering from coronary artery disease.

*Examination.* When seen in our clinic he revealed no evidence of organic disease. He had hypertrophied tonsils. He was not dyspneic or cyanotic. The heart was normal in size on percussion. The heart sounds were of normal quality and intensity, and there were no murmurs. The lungs were clear throughout. Spondylitis or arthritis of the shoulder joints could not be detected. The blood pressure was 120 systolic and 80 diastolic. There was no evidence of arteriosclerosis in the retinal,

radial, or dorsalis pedis arteries. Fluoroscopy revealed the heart and lungs to be of normal appearance. An electrocardiogram (Fig. 1A) was normal; there was but slight slurring of the QRS complex in lead 2. The vital capacity measured 4200 c. c., a normal figure for the patient's height and weight. His exercise tolerance, as measured by the two-step test (Master), was normal. The basal metabolic rate was also normal.

*Course.* In view of the history of a typical anginal syndrome on effort, it was considered at first that coronary artery disease was present, in spite of the youth of the patient. However, since no objective sign of cardiac disease could be elicited, either by physical examination or laboratory procedures, a functional basis for the patient's symptoms was sought. The patient was therefore referred to the Mental Health Clinic for psychiatric investigation.

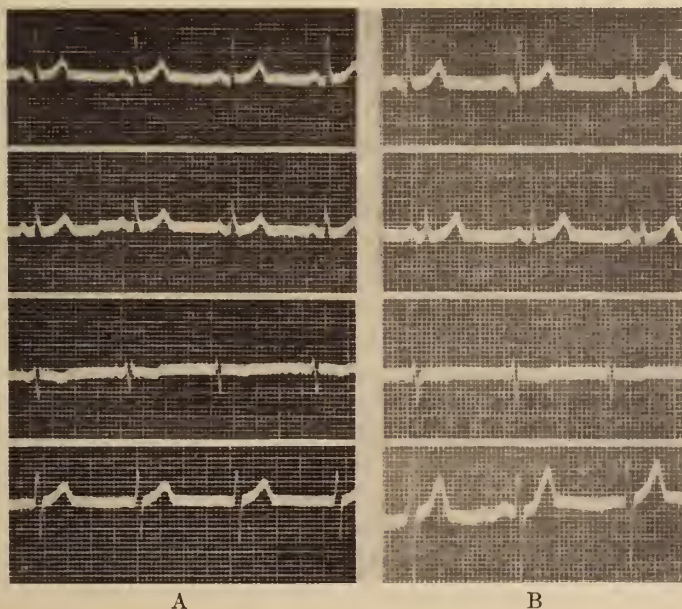


FIG. 1. A. December 19, 1934. Electrocardiogram shows left ventricular preponderance, slight slurring of the QRS complex in Lead 2, and a diphasic T-wave in Lead 3. There is no definite abnormality.

B. March 23, 1938. There is no change from the previous electrocardiogram.

*Psychiatric Investigation (Dr. Rose Spiegel).* The patient was a cloak-operator but had been unemployed for the past three or four years and was receiving Home Relief. He had three children, the oldest eight years of age. The two younger children suffered from frequent "fainting spells." In addition to the story of heart attacks obtained in the cardiac clinic, it was elicited that during the previous year the patient had been suffering also from nervousness and fainting spells. It was also determined that his first attack of chest pain had occurred immediately after seeing his youngest child brought in during an attack of syncope and apparently dead. This suggested a psychic component in his symptoms. Although only 29 years of age, he had the appearance of a man of at least 35. It was difficult at first to establish contact with him because he reiterated repeatedly his belief that he had an organic disease. He did not see any reason for attending a Mental Health Clinic

since he had been originally treated as a case of coronary occlusion. The patient was garrulous and expansive and his responses to questions were non-specific. Yet he was intelligent and he stressed his mental ability. He claimed that he had had ambitions to be an actor when he came to this country but had had to seek a job to support his family. He placed himself in the same category as the actor Paul Muni. It was the impression of the psychiatrist that the patient was suffering from a conversion hysteria and that this was the origin of the complaints referable to his heart.

*Further Course.* The diagnosis of a functional and psychic cause for the anginal syndrome has been corroborated by further observation of the patient during the past four years. In addition to the precordial pain he developed dizzy spells, numbness, and a nervous shaky feeling in his hands. His left arm felt "paralyzed". He continued to have precordial and sternal pain radiating to the back and left arm which became more or less constant, but was aggravated by exertion. Physical examination remained entirely normal. The electrocardiogram (Fig. 1B), which was repeated at frequent intervals, showed no changes from the original one. Several further attempts to test his exercise tolerance failed because he claimed that he developed faintness and chest pain after walking three steps. He also claimed that he was unable to perform a vital capacity determination. The patient developed numerous neurotic trends, became uncoöperative, and at times unmanageable.

#### DISCUSSION

Although the anginal syndrome for which the patient presented himself was characteristic of coronary artery disease and at one time was actually diagnosed coronary occlusion by a cardiologist, it is obvious now, after four years, that it was merely the first symptom in what later became a well-established neurotic complex. Several types of precordial pain are admittedly psychogenic, and there is no reason *a priori* why angina of effort may not occasionally fall also into this group. To be sure, it is often difficult to prove that, in addition, the coronary arteries are not involved. In the case cited there is almost certainly no organic heart disease, for, after four years, the physical examination and all laboratory tests are normal. We are cognizant of the claim of some authors that angina pectoris due to coronary artery disease may be present in the absence of confirmatory evidence of any kind. However, we believe that this is rare if all tests are considered, particularly after a period of several years of observation. While the physical examination of the heart, fluoroscopy, electrocardiogram, exercise tolerance, and vital capacity may individually remain normal, it is very improbable that all of these will do so. It is noteworthy also that the patient was only 29 years old when his symptoms began; although coronary disease may be present at this early age, it is uncommon. On the other hand, the greatest number of instances of cardiac neuroses occur between the ages of 30 and 40 years.

The mechanism of pain in coronary artery disease has been a subject of study for many years. It has been generally accepted that it is due to anoxemia and ischemia of the heart. In the presence of sclerotic coronary arteries, the increased work of the heart during exertion leads to impaired oxygen supply and transient myocardial ischemia. However, a nervous



mechanism is equally important, as a number of authors (2-7), as well as ourselves (8), have emphasized. Even when organic coronary artery disease is present, the frequency and severity of the anginal syndrome are greatly influenced by mental and emotional factors, or in the words of Heberden, "by passionate affections of the mind." Two patients with similar degrees of coronary artery disease may suffer pain of very different severity, depending upon the psychic make-up of each patient, and whether he is "hyper-" or "hypo-sensitive." Furthermore, many post mortem observations in persons with a severe anginal syndrome have revealed meager abnormal changes in the heart. On the other hand, it is not rare to find advanced coronary sclerosis at necropsy in the absence of an anginal syndrome. The necessity of a nervous sensitivity of the patient in the production of pain is thus evident. This being true for patients with heart disease, it is not unexpected that precordial pain may occur in the absence of heart disease. Psychiatrists have emphasized the importance of the heart as the "specific sense organ of anxiety" and the close interrelation of the brain with the innervation of the heart. And indeed, precordial pain is often the major symptom of a neurosis without organic basis. While the pain of organic heart disease is usually related to effort, not infrequently such an association is lacking. And there is no reason to believe that pain of psychogenic origin may not come on with effort occasionally. Exertion produces changes in pulse rate and contraction of the heart which may be experienced as pain sensations by susceptible persons, as was the case in the patient presented. It is thus sometimes impossible to differentiate an anginal syndrome of organic origin from a functional one by the type of pain and its relation to effort.

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# DEFICIENCY SYNDROME AND DIFFUSE INFLAMMATION OF THE CENTRAL AND PERIPHERAL NERVOUS SYSTEM

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[From the Neurological Service of Dr. I. S. Wechsler]

The following case is of interest not only because of the unusual clinical picture, but also because it illustrates so well the complexities of neurological diagnosis which are often encountered.

## CASE REPORT

*History* (Adm. 433764). A 54 year old, white, native-born housewife, was admitted to The Mount Sinai Hospital on December 20, 1938, with a history of having been unable to move any of her extremities since June, 1938.

Her family history was negative, except that a sister and a brother had both died in their forties of "enlargement of the heart and complications." Her past history revealed the following relevant facts. In 1921, prior to an operation for ovarian tumor, she was discovered to have "heart trouble," for which she had since been occasionally treated with digitalis. In 1925, she had had an attack of "sciatic rheumatism," characterized by pain in the lower spine and shooting pains down the back of both thighs, which completely subsided after two months of bed rest. She had had belching and an intolerance for fried foods for many years, but her appetite was good and her diet was balanced and adequate. All her teeth were removed in 1936, because of pyorrhea. There was no history of exposure to any toxic substance.

In 1934 the patient began to have frequent attacks of vertigo and occipital headache, which were not related to any known cause, and which gradually subsided spontaneously after two years. Her blood pressure, taken at this time, was said to have been normal. During most of 1937 she felt entirely well. In October of that year, however, the same attacks began to recur, and at the same time the patient noted a constant feeling of numbness along the outer surface of the right foot. This gradually extended up the lateral aspect of the leg to the knee. Simultaneously, the patient noted that she was beginning to drop objects from her right hand rather frequently. Three weeks after the onset of numbness in this right leg, weakness also appeared in the limb, and progressed so rapidly that in a few days the patient could not lift it going upstairs. She also began to have some pain in both legs. One week later, on Thanksgiving Day, 1937, while at dinner, she suddenly dropped her fork, fell forward on the table, and began to vomit. She did not lose consciousness but was unable to speak clearly. In addition the right side of her face was drawn up, and her right eye was closed. She was put to bed, where she vomited frequently and complained of severe vertigo.

Two weeks later, on December 9, 1937, she was admitted to a hospital, where, because of her persistent vomiting, her diet consisted only of parenteral fluids for about eight weeks. Her blood pressure then was noted to be 190 systolic and 110 diastolic. Her deep reflexes were all markedly diminished. There were no pathological reflexes. All of her limbs were weak, the right more so than the left. She developed a transient diplopia on left lateral gaze. Her spinal fluid was clear and under normal pressure, with 8 cells per cu. mm. Spinal fluid proteins were negative.

Other laboratory findings, including gall-bladder X-rays, were negative except for a leukocytosis of 15,450 on admission, which gradually subsided to 8,200. Near the end of January, 1938 the patient spontaneously began to regain her strength, and on discharge from the hospital on February 15, was much improved. By March she was able to walk about fairly well, and to climb stairs without much difficulty.

On April 10, 1938, however, vomiting and diplopia recurred, and her legs began to weaken again. In addition she began to have marked shortness of breath, which was relieved by the administration of digitalis. The weakness rapidly progressed, accompanied by severe burning pain and some edema in all her extremities, so that by the end of June, she was completely paralyzed in all four limbs. During July the pain in the extremities was so severe that she could not bear to be touched. She remained in this condition with little change, until her admission to The Mount Sinai Hospital in December.

*Examination.* The patient was a chronically ill, middle-aged woman, afebrile and bedridden. Her skin was shiny, smooth, and atrophic, and there were thick, yellowish areas of hyperkeratosis measuring one-eighth of an inch in thickness in some places, on the lateral aspects of the fingers. The heart was markedly enlarged, and there was a loud systolic murmur heard over the precordium and transmitted into the axilla. The rhythm was regular. The blood pressure was 160 systolic and 100 diastolic and there was moderate peripheral arteriosclerosis. The lungs were clear. The abdomen had a somewhat doughy consistency to palpation. There was moderate pitting edema of the lower extremities. In the median portion of the lower conjunctiva of each eye were small grayish-white areas, which were thought by some observers to resemble Bitot's spots.

Neurological examination revealed a complete flaccid quadriplegia. Slight movement was possible at the hips and shoulder joints. There was generalized muscular wasting and atrophy, with no fibrillations. None of the deep reflexes, or abdominal reflexes, could be elicited. There was marked tenderness on pressure over the muscles, bones, joints, and skin of the extremities, and less marked tenderness over the trunk. Cotton-wool perception was diminished in both sock areas, and to a lesser extent in both glove areas, more so on the right. Pin-prick showed patches of diminished sensation in the same areas, as did temperature sensibility. Vibratory sensation was absent in the feet and right hand, and diminished below the iliac crests and in the left hand. Position sense was slightly impaired in both feet, and in the right hand. Cranial nerves were normal except for a slight left external rectus weakness, and atrophy and fibrillations of the right half of the tongue. The tongue deviated to the right.

*Laboratory Data.* Red blood count, 5,700,000; white blood count, 14,000 (polymorphonuclear neutrophils, 61 per cent; lymphocytes, 36 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent; monocytes, 1 per cent). Blood Wassermann reaction, negative; blood sugar, 90; urea nitrogen, 13. Urine analysis, negative. Gastric analysis showed the presence of free hydrochloric acid. Spinal tap yielded clear fluid under an initial pressure of 160 mm. of water; final pressure, after the removal of 10 c.c., was 80 mm. of water. Pandy reaction was 4 plus; there were 2 mononuclear cells. Total protein, 157 mg. per cent; Wassermann reaction, negative. Colloidal gold curve was entirely negative. Muscle and skin biopsy taken from the right thigh revealed foci of lymphocytic infiltration in the muscle. The skin was normal.

*Course.* The patient was afebrile throughout her hospital stay. Respirations were normal. Pulse was regular and ranged between 76 and 108 beats per minute. On December 28, eight days after admission, the patient was placed on a high vitamin diet, and received in addition 3,000 units of Vitamin B<sub>1</sub> daily, by intravenous route, and six carotene tablets daily. Under this regimen her general condition improved markedly; the areas of hyperkeratosis on the fingers rapidly cleared, and her pains

largely subsided. However, she showed no perceptible change in her objective neurological condition up to the time of her transfer to Montefiore Hospital in February, 1939.

#### DISCUSSION

The diagnosis in this case was complicated by the fact that in the course of her illness the patient underwent long periods of vitamin deprivation which, in itself, in extreme cases, is capable of causing a neurological picture similar to the one this patient presented (1). However, the fact that her first symptoms began prior to any history of dietary insufficiency and that a partial remission in her symptoms occurred at the time of her first hospitalization, *during a period of relative vitamin deprivation*, points to the existence of some other factor as the primary etiological agent. The evidences of diffuse involvement of the nervous system, from the neuraxis out to the nerve endings in the muscles, the history of remissions and exacerbations, the leukocytosis, and the albumino-cytologic dissociation in the spinal fluid, all indicate that we are dealing with a subacute process akin to that first described by Guillain and Barré under the heading of "Radiculoneuritis and Acellular Hyperalbuminosis of the Cerebrospinal Fluid" (2), and ascribed by them to a neurotropic virus. Despite the term "radiculoneuritis" by which they designated this condition, many of their cases, like the present one, showed evidence of more diffuse involvement of the nervous system, and some, also like the present one, showed evidence of muscle involvement so that they had to be differentiated from cases of polymyositis. It must be emphasized that the assumption of a neurotropic virus as the causative factor in these cases is purely hypothetical, and that the etiology is still obscure.

In the present case, the selectively greater involvement of the peripheral nerves, the peculiar skin lesions, and the history of prolonged vitamin deprivation, suggest that the underlying pathological process was aggravated by a superimposed deficiency syndrome. This impression was fortified by the rapidity with which the patient's skin lesions and pains melted away under vitamin therapy.

Periarteritis nodosa and dermatomyositis were also considered in the differential diagnosis of this case but were ruled out on clinical grounds.

Prognosis in cases of Guillain-Barré syndrome (a name, incidentally, which is not satisfactory, and which should be replaced by an anatomico-pathological designation) is usually good, but in cases like the one herein described in which the quadriplegia has persisted unchanged for so long, the outlook for recovery is less favorable. There is no specific treatment.

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## A CHEMIST LOOKS AT SURFACES\*

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Most people are able to give their height in feet, their weight in pounds, and their waist-line in inches, but when asked to give the measurement of their surface area, would hesitate—not because they are ashamed of it, but because they have never bothered measuring it. This relative ignorance is not confined to everyday life, but biology itself is not yet “surface conscious.” In biological investigations measurement of length or diameter, of weight or volume are incomparably more frequent than data on surfaces and areas.

Measurement and comparison of weights were of predominant importance as long as biological chemistry was mostly concerned with the study of the metabolism of nutriment, that is with the fate of the basic food materials, their utilization in the animal body, their conversion into heat and energy and their assimilation into animal tissue. Since the turn of the century biochemistry has encompassed new fields with rapid strides, so that chemists are now in the position to give to biologists and physicians detailed information regarding the chemical structure of numerous physiologically active substances such as vitamins, hormones, enzymes, toxins, etc., substances whose importance for life is not based on their energy content, as in the case of the fuel materials, but whose task it is to promote or catalyse biological reactions for the benefit of the living body. Reflecting on the nature of these reactions, the sum total of which means Life, we cannot help noticing that the great majority of them takes place at surfaces.

When a physicist looks at surfaces, he feels inclined to classify them according to the state of matter at both sides of the boundary which may separate (1) a gas from a fluid, (2) a fluid from another fluid, (3) a gas from a solid, (4) a fluid from a solid, and (5) a solid from another solid. For most of these combinations one may give biological examples, keeping in mind that the membranes of animal cells are usually covered with a fluid phase. In the lungs of higher animals the oxygen of the air is brought into intimate contact with the blood at the surface of the so-called alveoli; in the digestive tract, solid and liquid food materials are in chemical exchange with the digestive juices coating the lining of stomach and intestine; in

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the gills of fish, in the kidneys, and in many other organs, two fluids meet across a membrane; within the blood stream solid blood corpuscles are surrounded by the serum fluid, and so on. Considering the minute structures visible under the microscope, we notice that the gross surfaces referred to consist of villi in the intestine, of trabeculae in the bones, etc., and that the great variety of tissue and cell structures permits greater area development and mosaic-like variegation of living surfaces. Most fundamental processes of life, namely secretion, resorption, and, in particular, growth, occur along surfaces and between laminae. Thus it becomes useful and necessary for the biologist to become "surface conscious" and to inquire about quantities and qualities of surfaces, for instance, to learn that the area of the human digestive tract, which is about  $2 \text{ m}^2$ , is more than doubled by the accessory surface of the intestinal crinkles, that the total surface of the alveoli in the lung, through which we breathe, takes in nearly  $200 \text{ m}^2$  ( $2000 \text{ sq. ft.}$ ), and that the combined surface area of the red blood corpuscles in 5 liters of blood, the circulating volume of an adult, covers  $3000 \text{ m}^2$ , or more than three-quarters of an acre. In many instances a drug or a poison will be less effective, or less toxic per unit of body weight, in smaller than in larger animals. This is because the body weight of an animal runs parallel with the cube of its length, whereas surface areas, which we imply to be the field of action for these drugs, are proportional to the square of the length. Hence, man is to be considered not as one thousand times larger than a guinea pig on the basis of the relative weight or bulk, but as only one hundred times as big on the basis of the respective surface areas.

Atoms and molecules have gained so much reality in recent years, that chemists nowadays are not content with stating the molecular weight of a compound, but can measure the length, breadth, and width of a single molecule of it by methods of what may be aptly called "molecular anatomy" or "chemical dissection." This is accomplished by X-ray spectroscopy, by electron diffraction, and by the study of monomolecular layers or films—invisible films. The latter are formed on the surface of a liquid by various methods and are known to be just one molecule in thickness.

The study of invisible surface films on water dates back to the time when Benjamin Franklin, on his ocean passage, became interested in the calming of troubled waters by oil. His prestige at the Royal French Court as the first Ambassador of the United States was increased by his apparently magical powers, when he used to walk through palace gardens and calmed the ripples on the lakes by wielding his walking stick in which a supply of olive oil was concealed.

The modern development of surface chemistry destroys the popular conception of a chemist as that of a fellow in a white coat handling flasks, test tubes, and bulky alembics; he may still wear a white coat, but you may find him sitting in front of a tray or trough, the fluid in which is

covered on its surface by a monomolecular layer ("monolayer") of a chemical compound. A simple calculation will convince you that a monolayer of, say,  $25 \text{ \AA}$ , that is, one-tenth of one-millionth of an inch thickness, covering one square meter weighs less than 3 mg., or that one grain avoirdupois of such a layer will cover 300 sq. ft., i.e., the floor area of a good-sized living room. These figures can be checked by measuring the area of a monolayer obtained by spreading a weighed amount of substance. The chemist, if he has had, like the author, the privilege to acquire, through collaboration with Dr. Langmuir, the methods developed by Dr. Langmuir and Dr. Blodgett of building up such monolayers on chromium-plated slides, could then be seen holding such a slide vertically in his hand and moving it slowly down and up through the monolayer. This film, under suitable lateral pressure, then attaches itself on both sides of the slide, first on the downtrip and then again on the uptrip, and this game may be repeated with the film being folded up like one of the old-fashioned long round-trip railroad tickets. Eventually the resulting multimolecular film will reach a thickness comparable to one-quarter wave-length of visible light and produce brilliant interference colors, like those of oil on water which you may observe daily, say, near a gas station on wet pavement. The thickness of the multimolecular film can be accurately estimated by optical methods; from this thickness and the predetermined number of layers deposited the height of the individual monomolecular layer and that of the molecule may be calculated; in connection with its known molecular weight, the area which one molecule occupies may then be computed.

I think it will be quite useful for biologists and physicians, to correlate the data on surfaces of anatomical structures, for instance in the nervous system and the circulatory system, with the knowledge that one square inch of a monolayer of diphtheria toxin suffices to kill forty guinea pigs; or, for instance, that the red blood corpuscles contained in one c.c. of blood, in order to have their area (ca.  $7000 \text{ cm}^2$ ) completely covered with a monolayer of cholesterol, require about as much cholesterol as is contained in the dissolved state in the surrounding blood serum (2 mg.). This relationship is perhaps of importance in certain kidney diseases where the blood contains an increased amount of dissolved cholesterol, while the blood corpuscles display enhanced resistance against hemolysis. Hemolysis, the bursting of the red blood corpuscles, may be brought about by a number of various agencies acting by means of a variety of mechanisms. One of the hemolytically active classes of chemicals, the saponins, destroys red blood corpuscles in as high a dilution as 1:100,000. Now, if a monolayer of cholesterol is spread on a water surface and subsequently a saponin is injected, in the extremely high dilution mentioned, under the cholesterol film, then this film, which until now behaved like a "two-dimensional liquid," is rapidly penetrated from beneath by digitonin, its area increases,



and its viscosity rises to one million times the original value, giving it the consistency of a tough skin, though it is only one molecule in thickness. As we believe that the hull of blood corpuscles contains cholesterol facettes, profound alterations of the properties of that hull, when exposed to saponin, may be visualized, and changes in shape, permeability, tensile strength, and other vital properties must be anticipated.

The performance of model experiments, such as the penetration of a cholesterol film by digitonin, has been greatly facilitated and their scope expanded through the methods developed by Langmuir and his collaborators. Monolayers at the boundary between *fluid and gas* are most accessible for study, and allow the establishment of many fundamental physical laws and rules for "two-dimensional gases, liquids and solids." The adaptation of the conception of surface tension to the surface of individual molecules, and even to definite segments of the surface of a molecule, by Langmuir has led to the elucidation of many facts in two-dimensional chemistry.

*Gas-solid* interfaces may be studied by exposing built-up films to gases or vapors, but gas-fluid and gas-solid boundaries are less important for biological models than interfaces between *solids and fluids*, which may be studied by the submersion of built-up films under various conditions in liquids and solutions.

The determination of the contact angle of a drop of a fluid placed on a built-up film makes perceptible delicate differences and clears up important points in surface structure. Reactions of built-up films in liquids and solutions permit the study of chemical reactions of sterols with saponins, bile acids with fat, enzymes with their substrates, antigens with antisera, etc. Many systems of biological significance include proteins. These may in some instances be built up from monolayers spread on water, or otherwise by adsorption from solution on treated slides. The behavior of protein films is puzzling in many respects, but many of the observed facts harmonize with the theories of D. M. Wrinch of Oxford, that proteins consist of a two-dimensional network in hexagonal pattern which looks somewhat like a piece of wire netting. There are some indications in the behavior of protein films for the resultant dorsal-ventral asymmetry; that means that the upper and lower side of a protein film differ in their properties from each other, say, like the sides of a piece of velvet. Different sides of the protein film are absorbed to a slide depending on whether it has been conditioned with a polyvalent metal, such as thorium, giving a rather hydrophilic surface; or by deoxycholic acid, a bile acid with extremely oleophilic properties. The properties of protein layers are influenced by the nature of the underlying film; in turn, they influence the character of films built up on top of them.

There is considerable evidence that many proteins, e.g. insulin, pepsin, albumin, globulin, hemoglobin, virus proteins, etc., consist of globular



molecules of molecular weight uniform for each species of molecules. The unfolding of these globular proteins into protein films and the possible reversion of this process leave much space for speculation. But it is known definitely that all protein films, under identical lateral pressure, are of identical thickness, whereas protein globules vary in diameter from 30 to 300 Å. The globular proteins may also be adsorbed in monomolecular layers on conditioned surfaces, and with certain devices a uniform measurable thickness may be achieved which is in good agreement with the molecular weights estimated by Th. Svedberg with the ultracentrifuge. This adsorption method bears a resemblance to the adsorption methods using alumina and other metal hydroxides in sol form, but here, in the case of surfaces conditioned with basic aluminum or thorium stearate, the area of the adsorbing surface is accurately measurable and opens a new quantitative approach to enzymatic and immunological research problems.

The conditions on fluid-fluid interfaces are equally important for biology. Since the two fluid phases have no predetermined shape, the area and nature of the interface will be governed by the surface, or rather interface, tension of the two fluids. Whereas certain substances will accumulate in the interface, the amounts will usually be insufficient for monolayers of the "two-dimensional fluid" type and we have to deal mostly with so-called "Gibbs layers."

Surface tension, in turn, is strongly influenced by inorganic ions, and the study of these phenomena, for instance, by Jacques Loeb, Osterhout, Clowes and others, emphasizes the importance of inorganic chemistry for biology. The fate of an oil-water mixture will depend, according to Clowes, on the presence of alkali soaps promoting the dispersion of oil in water, or, on the other hand, of calcium and other bivalent ions, favoring the inversed emulsion, namely water in oil. *Fluid-fluid* interfaces are of the utmost significance in the resorption of lipoids and in the mechanism of enzymatic lipolysis, both in the digestive tract and in intracellular lipid metabolism. The activating function of the bile salts, of calcium and magnesium ion and of phosphatids calls for further investigations in this connection.

These examples may have demonstrated to you that we have won in the experimental study of monomolecular layers a new tool for studies in the fields of enzyme chemistry, immunology, and, in general, for the structural investigation of proteins and other megamolecules, chemical investigations which are of paramount importance in the study of, and the fight against, disease.

## EXPERIMENTAL ANTI-CANCEROUS IMMUNITY\*

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It is generally known that animals in which tumors have regressed spontaneously become almost resistant to further inoculations with the same tumor strain. It is obvious, then, that if it were possible to induce regressing growths by some means, the production of acquired anti-cancerous immunity would be materially advanced. Accordingly, an attempt has been made by Prof. Besredka and the author to produce regressing growth by a special method of implantation. Experiments which were carried out at the Pasteur Institute in Paris for several years can be summarized in the following conclusions:

### A. AFFINITY

1. The evolution of an implanted tumor does not depend only on the malignancy of the implanted tumor strain and on the inherited, natural resistance of the animal, but also on a third, important factor, the method of implantation.

2. Various tissues differ in affinity to the implanted neoplasms. The affinity of the tissue to the neoplasm is strictly proportional to the ability of the tissue to develop resistance to the induced disease. If the affinity is high, a small number of implanted tumor cells is sufficient to induce a tumor; but at the same time, if the corresponding reaction is sufficiently strong, the animal recovers and the tumor disappears spontaneously.

On the other hand, if the affinity of the tissue is low, a somewhat greater number of tumor cells is necessary to induce a tumor; but once the tumor "takes," it grows progressively with practically no resistance, or little resistance of the host, and kills the animal.

3. According to their affinity and proportional ability to develop resistance, the tissues can be ranged as follows: a) skin, b) subcutaneous tissue and muscles, c) stomach wall, d) testicles.

This is a very incomplete list, other organs having not yet been tested sufficiently. Experiments carried out in different species of animals and with different strains of tumors seem to indicate that this list is generally

\* Abstract of a lecture delivered at the Blumenthal Auditorium of The Mount Sinai Hospital, December 6, 1938.

applicable, no matter which species of animal or which tumor strain is used.

4. According to the affinity scale indicated above, the surest method of producing *regressing* growth is obviously an injection of a small amount of neoplastic cell emulsion into the tissue which has the highest affinity, and at the same time the highest ability to induce resistance: that is, into the skin.

Spontaneous regression of tumors implanted into other tissues, namely, under the skin, in the muscles, into the stomach wall, or even in the testicles, is possible, but always uncertain and unpredictable.

5. In the case of a very high malignancy of the implanted tumor strain in mice—for instance, the Ehrlich mouse sarcoma—pure inbred strains of animals, possessing a certain natural resistance, must be used in order to induce regressing skin tumors and bring out the difference between the benign intracutaneous and the dangerous subcutaneous implantation.

#### B. IMMUNITY

6. The spontaneous regression of a neoplastic growth—no matter where the tumor is situated—is, as a rule, the sign of the establishment of an acquired, anti-cancerous immunity.

7. A recovered animal is almost entirely resistant to a second implantation of the same tumor strain. This immunity is generally specific, directed only against a single tumor strain; but in some cases cross immunity toward two histologically different tumor strains can be observed.

8. In order to induce immunity, the implantation of the tumor must be followed by the formation and subsequent disappearance of a real, neoplastic growth. Both conditions must be fulfilled. If the animal does not react to the first inoculation, no immunity follows.

9. The complete disappearance of the tumor, though secondary, is the only dependable symptomatic sign of the establishment of a general immunity of the host, which shortly precedes the disappearance of the growth. Therefore:

10. The regression of the tumor must be spontaneous. Its removal by excision or electro-cautery or its healing by radium, does not induce immunity.

#### C. THE NATURE OF THE IMMUNITY

11. The acquired, anti-cancerous immunity is not transferable to normal animals even by injection of a very large amount of immune serum or by parabiosis. This seems to indicate that the immunity does not depend on the presence of specific antibodies in the blood serum but that it is of a cellular nature.

## CLINICAL PATHOLOGICAL CONFERENCES

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, October 19, 1938*

*Case 1.* Primary Colloid Carcinoma of the Stomach, thirteen years after resection of a sphenoïdal cell carcinoma of the stomach

*(From the Medical Service of Dr. George Baehr)*

*History* (Adm. 425793; P.M. 10846). This patient, a sixty-one year old male, was operated upon in this hospital thirteen years previously, when a subtotal resection of the stomach was done for a sphenoïdal cell carcinoma. Following the operation the patient was treated with X-ray therapy. Three years before admission he experienced a series of attacks of precordial pain relieved by nitroglycerine. Four weeks before hospitalization, the patient noted abdominal pain, most marked in the left lower quadrant, abdominal distention, and anorexia. These symptoms persisted up until May 1, 1938, when he was hospitalized.

*Examination.* The patient showed evidence of recent weight loss. The abdomen was diffusely tender and a large mass, considered to be the liver, was felt in the right upper quadrant. This mass was stony hard and moved slightly with respiration. On rectal examination, a firm transverse ridge without mucosal ulceration was felt above the prostate gland.

*Laboratory Data.* The blood hemoglobin was 82 per cent (Sahli) and the white blood count was 12,000 cells per cu. mm. with a normal differential count. The blood urea was 13 mg. per cent and the sugar, 100 mg. per cent. The Wassermann test was negative. The urine showed a faint trace of albumin and a rare granular cast. An electrocardiogram demonstrated changes suggestive of myocardial disease. The stool was guaiac positive; the Rehfuß test meal showed no free acid but blood was present in the aspirated material. Sigmoidoscopy was performed and a constriction was noted at 15 cm. Several polyps were seen in the rectum. A barium enema showed multiple filling defects involving the splenic flexure, the proximal, sigmoid, and descending colon.

*Course.* A diagnosis of intra-abdominal inoperable malignancy was made. The patient vomited continuously while in the hospital and he died two weeks after admission.

*Necropsy Findings.* An infiltrating cylindrical cell carcinoma of the stomach was present, arising about one inch proximal to the operative stoma. There were diffuse peritoneal metastases.

*Comment.* *Dr. Klemperer:* This neoplasm is a new one and not a recurrence of the lesion removed thirteen years ago. The histology of the two tumors is different and the time interval since the last operation is very long.



*Dr. Baehr:* The diagnosis of a carcinoma of the stomach should have been made clinically because of the presence of blood in the aspirated gastric contents. A more precise location of the intra-abdominal malignancy could have been made.

Reported by *Abner Kurtin, M.D.*

*Case 2. Rupture of Syphilitic Aortic Aneurysm into the Pericardial Sac*

*(From the Medical Service of Dr. B. S. Oppenheimer)*

*History* (Adm. 368991; P.M. 10876). The patient, an Italian male, was admitted to the hospital for the first time on July 21, 1934. Four days before admission he vomited and had right upper quadrant pain radiating through to the back. Examination at that time revealed an obese male with an indefinite mass and resistance in the right upper quadrant. The Wassermann reaction was 4 plus. He was icteric and bile was present in the urine. After five days he became asymptomatic. A gall bladder X-ray series was then done according to the Graham technique which showed non-visualization of the viscus. He was believed to have a cholecystitis, but because of his obesity and the complete disappearance of symptoms, it was thought advisable to withhold surgery. He was discharged from the hospital and remained well for three years when he began to note precordial pain and slight dyspnea on exertion. During this interval he received anti-luetic treatment. He was then readmitted on November 14, 1937 for one day because of an impacted fracture of the right humerus. At about this time he began to note ankle edema. For two weeks before his last admission, on August 1st, 1938, he experienced repeated attacks of hypogastric pain. During the week before admission he had two shaking chills and for these complaints he was admitted to the hospital.

*Examination.* The patient was obese and slightly icteric. The neck veins were dilated. The chest was emphysematous with moderately increased retromanubrial dullness. There were bilateral basal râles. A systolic murmur was present at the apex of the heart and at the aortic area and the second aortic sound was louder than the second pulmonic sound. The blood pressure was 100 systolic and 60 diastolic. There was tenderness and rigidity in the epigastrium and right upper quadrant.

*Laboratory Data.* The blood hemoglobin was 84 per cent and the white blood count, 7,300 cells per cu. mm. with a normal differential count. The galactose tolerance test was normal. The stool was guaiac-negative. No bile was found in the urine. The blood chemistry reports were: urea nitrogen, 14 mg. per cent; sugar, 90 mg. per cent; total cholesterol, 215 mg. per cent, with 40 per cent ester; icteric index, 8; blood Wassermann reaction, negative. An X-ray examination of the chest revealed hypertrophy and dilatation of the left ventricle with dilatation of the transverse and descending aorta. Electrocardiogram showed left ventricular preponderance.

*Course.* The patient's abdominal symptoms disappeared after five days. Be-

cause of the X-ray evidence of aortic aneurysm, a laryngoscopic examination was done which revealed evidence of a left recurrent laryngeal palsy. On the sixth day of his admission, the patient suddenly became cyanotic and pulseless and he died a few minutes after the onset of this episode.

*Necropsy Findings.* There was chronic cholecystitis and cholelithiasis. Syphilitic aortitis of the arch and descending aorta was noted, with an aneurysmal dilatation of the arch which was filled with lamellated clot. The aneurysm had ruptured into the pericardial sac and within this sac were 500 c.c. of clotted blood. The aneurysm had mainly presented itself posteriorly, partially obstructing the pulmonary arteries with the production of hypertrophy of the right ventricle.

*Comment.* *Dr. Baehr:* This patient's longstanding peripheral edema and other signs of right heart failure were probably caused by pressure of the aneurysm upon the pulmonary vessels. This could have been suspected clinically.

Reported by *Abner Kurtin, M.D.*

*Wednesday, October 26, 1938.*

*Case 1. So-called Plasma Cell Myeloma with Infiltration  
of Periosseal Tissues*

*(From the Medical Service of Dr. B. S. Oppenheimer)*

*History* (Adm. 422892; P.M. 10777). The patient was a forty-seven year old white male who had a previous admission to the hospital (October 1932) for acute, gangrenous appendicitis with abscess formation. Appendectomy was then performed. His convalescence was uneventful. During that admission, repeated urine examinations were negative for albumin. In November 1938, he was re-admitted because of a seven month history of intermittent pain in the posterior region of both hips radiating to the popliteal spaces. For the past five months there had been bilateral diminution of vision. Four months ago, urine analysis revealed albuminuria. Anemia was discovered at that time. His diet was then restricted by his physician, with elimination of meats, vegetables, and salts. There subsequently developed weight loss, weakness, low back pain, increased urinary frequency and nocturia.

*Examination.* The patient was poorly nourished, pallid, and showed evidence of recent weight loss. The optic discs were pale, but there were no retinal hemorrhages or exudates. The heart and lungs were normal. The edge of the spleen was palpable 2 cm. below the costal margin. Liver edge was not palpable. There was tenderness over the sterno-xyphoid junction, lower thoracic spines and over the fifth lumbar vertebra. The left suprapatellar and patellar reflexes were diminished. The ankle jerks were equal.

*Laboratory Data.* Urine was alkaline; specific gravity, 1.026; there were 16 grams of albumin per liter; sugar was negative; sediment contained occasional hyaline and granular casts, and rare red blood cells. Repeated examinations of the urine for Bence-Jones protein were negative. Blood urea nitrogen, 8 mg. per cent; sugar, 100 mg.; icteric index, 1; blood cholesterol, 220 mg.; ester, 63 mg.; phosphorus,

4.2 mg.; calcium, 10.3 mg.; phosphatase, 18.5 King-Armstrong units. Total protein, 5.4 per cent; albumin, 2.9 per cent; globulin, 2.5 per cent. Blood Wassermann negative; hemoglobin, 42 per cent; 3,250,000 red blood cells; 420,000 blood platelets per cu. mm.; white blood cells, 6,800 with a normal differential count except for the presence of 1 myeloblast, 1 plasma cell, and 1 normoblast per 100 white cells. There was a moderate amount of rouleaux formation, less marked than is usually found in multiple myeloma. Autoagglutinins were not present.

Sternal marrow aspiration revealed 60 per cent plasma cells. X-ray showed a moderate degree of decalcification of the skull and long bones with coarsening of the trabecular pattern.

*Course.* The patient was given two citrate transfusions with a rise in hemoglobin to 60 per cent and clinical improvement. He was discharged with a diagnosis of multiple myeloma.

*Third Admission.* He was readmitted three weeks later because of progressive anemia. An X-ray examination of the skull and long bones showed a slight advance in osteoporosis. He was given a 700 c.c. transfusion and discharged.

*Fourth Admission.* Since the patient's discharge from the hospital, his course had been steadily downhill. He had become progressively weaker. The pain now extended throughout the entire spine. An increase in urinary frequency was noted and vision had become poorer.

*Examination.* The patient appeared chronically ill and pale. There was moderate proptosis of the right eye with widening of the palpebral fissure. Nerve deafness was present on the right side. The spleen now extended 4 cm. below the costal margin, and the liver edge had become palpable at a point 6 cm. below the costal margin. The urinary bladder was distended to the level of the umbilicus. The back was held rigidly and percussion tenderness was present over the spine and sacrum. There was moderate droop of the right side of the face; deep reflexes were hyperactive; lower abdominals were absent; upper abdominals easily exhausted; Babinski and Rossolimo were elicited on right; there was moderate loss of position sense in the toes and foot.

Urine analysis revealed 4 plus albumin with only a few red blood cells and occasional granular and cellular casts. The ordinary heat test was again negative for Bence-Jones protein, but the sulphosalicylic acid test suggested the presence of these bodies. Residual urine was 18 oz.; blood phosphorus, 6.6 mg.; calcium, 12.5 mg. per 100 c.c.; phosphatase, 19 King-Armstrong units per 100 c.c.; total protein, 7.8; albumin, 5.3; globulin, 2.5. Hemoglobin was 52 per cent; red blood cells, 3,500,000; white blood cells, 7,700 with 50 per cent polymorphonuclear leucocytes; 2 per cent eosinophiles; 36 per cent lymphocytes; 12 per cent monocytes. Blood urea nitrogen was 16 mg. per 100 c.c.

*Course.* There was gradual increase in weakness. The neurologist confirmed the impression of compression myelopathy with secondary sphincteric disturbances. Lumbar puncture showed almost complete block. The fluid was slightly xanthochromic and the Pandy test was 4 plus; total protein was 235 mg. per cent. Roentgenograms of the skull and lumbar spine showed numerous areas of rarefaction, most marked in the body of the fourth lumbar vertebra. In view of the increasing distension of the bladder, a catheter was left indwelling for three days. Temperature began to show daily rises to 102°F. Despite two transfusions, his temperature mounted steadily. He died nine days later, eight months after the onset of his complaints.

*Necropsy Findings.* Throughout the *vertebrae*, *sternum* and *ribs* there were soft, grayish nodules, rather sharply outlined, replacing the normal bone marrow and destroying the trabeculae. The process in the third lumbar vertebra was so extensive that it resulted in complete destruction. Further, the tumor tissue had broken

through the confines of the bone and had infiltrated the surrounding fissure and muscles, and had formed a mass along the left lumbar plexus. One of the ribs showed bulging of a nodule limited only by the periosteal layer. The extent of the pathological process was indicated by involvement of the ossified thyroid cartilage.

The *urinary bladder* was distended, showing a severe necrotizing cystitis.

The *spleen* weighed 275 grams. The moderate enlargement was a result of extra-medullary blood formation.

The *kidney* surfaces were irregular due to alternating nodular elevations and scattered depressions. The *pelves* showed acute inflammation. Microscopically, there was evidence of coagulated proteins in the tubules and dilatation and atrophy of the portions of the tubules proximal to the sites of obstruction. Foreign-body giant cell reaction surrounding the areas of coagulated proteins was observed.

Microscopic sections of the nodular infiltration of the bone marrow showed cells which resembled the plasma cell with its eccentric nucleus, but without wheel structure and basophilic cytoplasm. Some of the cells were very large and occasional multinucleated giant cells could be seen.

*Comment. Dr. Baehr:* The striking discrepancy between the marked albuminuria and the relative paucity of formed elements in the urine is an important point in differentiating this condition from chronic diffuse glomerulonephritis. The significance of a huge serum phosphatase as evidence of the presence of destructive bone disease should be stressed.

*Dr. Klemperer:* This is a case of myelosarcoma rather than a multiple myeloma, since in the latter condition the lesion is limited to the bone, whereas in this case, the pathological process was of a more aggressive nature, had broken through the bony confines and infiltrated the surrounding tissue. Nevertheless, the bone changes are identical in both entities. Furthermore, the so-called "plasma cell" of multiple myeloma is not a plasma cell, but merely resembles this structure in its eccentrically placed nucleus and basophilic cytoplasm. The striking variation in size and the occasional multinucleated giant cells definitely differentiate the two. The importance of this is that, were the cell a true plasma cell, then one would have to consider multiple myeloma an inflammatory, rather than a neoplastic, disease.

The mechanism of the renal impairment often observed in multiple myeloma can be explained as a result of the plugging of the lumen of the tubules with coagulated albumin, presumably of the Bence-Jones type. This becomes inspissated and stagnant; a foreign body giant cell reaction and obstruction ensue. The obstruction leads to proximal dilatation and, eventually, destruction, a process which has aptly been called internal hydronephrosis.

*Dr. Baehr:* In this connection, I wish to mention that a similar type of tubular obstruction by casts can occur in any severe albuminuria, including acute diffuse glomerulonephritis, as Ponfick originally reported. However, it is much more characteristic of multiple myeloma.

Reported by *Max Ellenberg, M.D.*



*Case 2. Congenital Hemolytic Icterus Associated with Multiple Venous Thromboses after Splenectomy*

*History* (Adm. 423106; P.M. 10793). The patient, a white female, was first admitted to this hospital in January, 1935, at the age of 31. Appendectomy had been performed nine years previously. About five years before admission, she began to note pallor which gradually increased and became associated with asthenia. One year before admission icterus was observed and the patient began to suffer with dyspnea on exertion, increasing asthenia, palpitation, occasional ankle edema, and episodes of vertigo and faintness. At this time she entered another institution where the diagnoses of pernicious anemia and hemolytic icterus were made. She was treated with transfusions, iron, and liver, with improvement; her hemoglobin rose from 22 to 62 per cent. She remained well for about a year, when her symptoms recurred. She re-entered the same institution and again received transfusions. The patient then returned to The Mount Sinai Hospital for a splenectomy. There had never been any purpuric manifestations or febrile episodes. The urine had always been dark brown. Investigation of siblings failed to reveal hematological abnormalities.

*Examination.* The patient was a chronically ill female with subicteric tint to the skin and sclerae. The icterae were pale. Pharynx was pale. Heart was not enlarged; a loud systolic murmur was heard over the precordium. Blood pressure was 120 systolic and 64 diastolic. The spleen was firm, sharp-edged, and palpable at a point level with the umbilicus. A sharp-edged liver descended to the same level. There was no ascites. Pelvic and rectal examinations revealed no abnormalities.

*Laboratory Data.* Hemoglobin, 41 per cent; red blood cells, 2,500,000; platelets, 400,000 per cu.mm.; white blood cells, 12,300 per cu.mm. (67 per cent polymorphonuclear leucocytes, 28 per cent lymphocytes, 3 per cent eosinophiles, 2 per cent monocytes). Reticulocytes, 76 per cent. A few normoblasts and a moderate degree of basophilia were noted. Bleeding time, 1 minute; coagulation time, 14 minutes. The tourniquet test was negative. Fragility test showed partial hemolysis at 0.56 to 0.4 and complete hemolysis at 0.36 per cent saline solution. Urine analysis was negative except for a positive urobilin in a 1:40 dilution. Blood Wassermann reaction was plus-minus and the Kahn test, 2 plus on two occasions, although these tests were negative in the husband. The blood urea nitrogen was 10 mg.; bilirubin, 0.6 mg.; cholesterol, 160 mg.; cholesterol ester, a trace; total protein, 7.4 per cent; albumin, 5.5 per cent; globulin, 1.9 per cent; icteric index, 18. A minimum amount of tyrosine was in the urine. Urinary urobilin was 21 mg. Stool was guaiac negative. Duodenal drainage revealed dark brown bile and occasional cholesterol crystals.

*Course.* In view of the positive Wassermann and Kahn tests, a course of anti-luetic therapy was instituted. During this time the patient's condition became progressively worse, the hemoglobin falling to 34 per cent. As a pre-operative measure, patient received a 500 c.c. blood transfusion by the Unger method. There was a severe chill, rise in temperature, a drop in hemoglobin, and an increase in icterus. The urine, however, remained guaiac negative.

Splenectomy was performed and a transfusion administered. The spleen was characteristically and intensely hyperemic, the normal histological appearance being obscured. Microscopically, the pulp spaces were full and the sinuses collapsed. Evidences of blood destruction were present.

The patient improved considerably postoperatively with the hemoglobin ranging about 45 per cent. Two weeks later she developed a phlebitis of the right forearm and began to have fever. The white cell count rose to 20,000, with 84 per cent polymorphonuclear leucocytes. The hemoglobin fell to 29 per cent. The blood platelets rose to 1,350,000 per cu.mm.; reticulocytes were 12 per cent, and normoblasts, 1 per cent. Howell-Jolly bodies were observed on smear. Hemoglobin value continued to decrease and another transfusion was given which resulted in a febrile reaction and increase of the icterus. The icteric index rose to 35. There were several episodes of sudden chest pain unaccompanied by cough, hemoptysis, cyanosis, or dyspnea. Roentgenological examination failed to reveal any evidence of pulmonary infarction. One month later she developed a phlebitis of the left subclavian and left innominate veins with swelling of the left upper extremity and edema extending to the left axilla and loin. A septic type of temperature continued. Blood platelets were now 470,000 per cu.mm.

The patient continued to do poorly and developed vague abdominal pain, tenderness and diarrhea, without blood in the stool, which was ascribed to an intra-abdominal vascular thrombosis. These symptoms gradually cleared. The patient was discharged two and one-half months postoperatively, definitely improved. At that time, the fragility test values remained as on admission, the Wassermann and Kahn tests were negative, the hemoglobin was 72 per cent, and the blood platelets had fallen to 210,000 per cu.mm.

*Second Admission.* The patient was perfectly well for a period of two years. In February, 1937, she suddenly developed nausea, vomited a pint of fresh blood, and passed into a state of mild shock with rapid, thready pulse and a blood pressure of 70 systolic and 30 diastolic. Dilated veins were noted along the right side of the abdomen.

*Course.* Several large hematemeses occurred after admission and the patient was given 1,000 c.c. of blood. It was felt that the bleeding was due to a ruptured esophageal varix secondary to a splenic vein thrombosis. The stool, which was tarry on admission, gradually became negative to guaiac. An X-ray examination of the esophagus showed the presence of varices. She did well on a Meulengracht diet, the hemoglobin rising to 65 per cent. The blood platelets were 660,000 per cu.mm. with 12 per cent reticulocytes. Two days before discharge a superficial vein thrombosis occurred in the right antecubital fossa. A sister was now found to have increased fragility of the red cells. On the basis of this, the clinical diagnosis was altered from acquired to congenital hemolytic icterus.

*Third Admission* (April 1938). For one year following discharge, the patient was in an excellent state of health. On the day of re-admission, she suddenly vomited a pint of bright red blood. She re-entered the hospital in a state of collapse. A venous hum was audible in the region of the ninth rib along the right rectus border. There were no other pertinent physical findings. The hemoglobin was 54 per cent; reticulocytes, 1 per cent, platelets, 240,000 per cu.mm. Stools were guaiac positive. Blood Wassermann reaction was negative. The erythrocyte fragility test was normal.

*Course.* The hematemesis recurred and evidence of oozing persisted. She was therefore given a blood transfusion. A second transfusion was given with Type I blood, compatible by direct matching (patient was Type II), following which the patient had a severe reaction manifested by nausea, vomiting, icterus, and hemoglobinuria. Compatibility of the blood was rechecked and confirmed. However,

agglutination titers of the donor's serum showed Anti-A agglutinins 1-512 (normal 1-100) and Anti-B of 1-128 (normal 1-60). Hence, it was felt that the transfusion reaction was due to the high Anti-A agglutinin titer of the donor. The urine was consequently alkalinized promptly. Another hematemesis necessitated another transfusion. This time Type II blood was used, and again a reaction occurred with hemoglobinuria and increased icterus.

In view of the persistent hematemeses, sclerosing solution (0.5 c.c. of 5 per cent sodium morrhuate solution) was injected into a sac-like esophageal varix, through an esophagoscope, as a last resort. However, the patient continued to bleed and, in spite of the administration of more than 5,000 c.c. of blood in four days, finally succumbed.

*Necropsy Findings.* The *esophagus* showed the presence of dilated varices. One varix, just above the cardia, was thrombosed and bulged into the lumen. Microscopically, one could see that this dilated vein had perforated through the epithelium. On opening the portal vein, which felt thickened, there was found much ridging, with bridges crossing the lumen of the vein. Attempts to pass a probe resulted in considerable obstruction. There was no evidence of a recent thrombus. A similar finding was present in the upper portion of the superior mesenteric vein, as well as the splenic vein. The splenic vein was narrowed throughout its course. Leading into the left branch of the portal vein was a markedly dilated umbilical vein, running in the falciform ligament from the umbilicus.

The remaining pertinent necropsy findings were of special interest because of the transfusion reaction. There were conspicuous foci of agglutinated erythrocytes within the *liver sinuses* and striking hemoglobin nephrosis with hemoglobin casts within the excretory tubules of the *kidney*. A solitary pigment stone of the *gall bladder* was found, as observed frequently in hemolytic icterus.

*Comment.* *Dr. Bachr:* I wish to call attention to the presence of the classical hematological findings of hemolytic icterus presented by this patient, i.e., the increase in fragility of the red blood corpuscles, the high reticulocyte count, and the presence of normoblasts and basophilia as evidences of blood regeneration. The presence of macrocytosis and a high hemoglobin index is compatible with the diagnosis of hemolytic icterus. In the presence of clinical evidences of hemolytic anemia, it did not warrant the early diagnosis of pernicious anemia. The positive Wassermann and Kahn reactions did not necessarily indicate the existence of syphilis in the presence of hemolytic icterus. False positive reactions are observed not only in hemolytic anemia but also in other diseases, such as lupus erythematosus. I wish to stress the importance of examining the total three-day output of urine and feces for urobilin, for this is the measure of the amount of hemolysis.

The rise in blood platelets to more than 1,000,000 following splenectomy and the resulting thrombosis of the splenic and portal veins should also be noted. This complication could probably have been anticipated, for even before the splenectomy, the blood platelet count ran above 400,000. Death was due to the late sequela of the postoperative portal vein thrombosis, hemorrhage from esophageal varices. It is interesting to note again the occurrence of a *bruit* over the ensiform cartilage caused by the flow of blood through large collateral veins within the epigastrium.

*Dr. Rosenthal:* In answer to the question as to severe transfusion reactions following the administration of compatible blood, let me say that the three cases I have observed at this hospital had been the recipients of many transfusions. Careful studies have shown that the reactions are related neither to the O, A, B grouping, nor to the m, n grouping. I believe that the untoward effects are due to some other substance in the red cells, comparable to the above factors, as yet undetermined.

*Dr. Baehr:* In considering the secondary effects of incompatible transfusions, I wish to comment on the severe kidney damage that may ensue after severe intravascular hemolysis. Oliguria and renal insufficiency may last for long periods of time. This is due to the damaging effect of the precipitated hemoglobin on the epithelial cells of the renal tubules. I have demonstrated this experimentally, using potassium chlorate to induce the erythrocyte destruction. The hypothesis that the renal damage following hemolysis is due to plugging of the renal tubules by hemoglobin casts is disproved by the persistence of fixation of specific gravity and other symptoms of renal insufficiency for months after recovery.

*Dr. Klemperer:* I wish to emphasize the nature of the splenic changes. The findings were those of an active hyperemia, the increased engorgement being in the intersinusoidal pulp as contrasted with passive hyperemia, the latter being associated with engorgement of the splenic sinuses. Interestingly, a similar lesion may be produced in dogs by denervating the spleen. However, evidences of hemolysis are not present in the experimental reproduction.

*Dr. Rosenthal:* The development of the portal vein thrombosis is perhaps the most interesting feature of the case. Thrombosis in hemolytic icterus is a relatively rare occurrence, this being only the second case with this complication that has come under my observation.

Reported by *Max Ellenberg, M.D.*



## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Bile Salt Therapy in Gallbladder Disease.* H. DOUBILET, H. YARNES, AND A. WINKELSTEIN. Am. J. Dig. Dis. & Nutrition, 5:348, August, 1937.

The physiology of the biliary tract and of the entero-hepatic circulation of bile is reviewed, and the relation to the symptoms of gallbladder disease is discussed. Therapeutic results are presented in a series of thirty-eight cases which were treated by means of a low fat, low carbohydrate, gallbladder diet and by the administration of adequate amounts of pure bile salts. Sufficient bile salt was administered to enable the patient to have at least one, and no more than two, bowel movements a day. The patients were divided into three groups: (1) those suffering from the post-cholecystectomy syndrome, (2) cases in which stones were shown to be present in a normally functioning gallbladder and (3) cases in which the gallbladder was not visualized. The results in the first group were excellent, most of the cases being relieved of their symptoms. In the second and third groups a large proportion of the patients were relieved of their symptoms. A few patients who had an associated hyperacidity could be relieved by administering alkalies and atropine in addition to bile salts.

*Multilayers of Sterols and the Adsorption of Digitonin by Deposited Monolayers.* I. LANGMUIR, V. J. SCHAEFER, AND H. SOBOTKA. J. Am. Chem. Soc. 59: 1751, 1937.

Methods for the deposition of monomolecular layers of various substances on metal plates are described and their properties discussed. Auxiliary methods are described for the measurement of the thickness of such films by means of the tilting angle and minimum refraction for monochromatic light, for the measurement of contact angles of liquids on deposited monolayers and for the determination of two dimensional viscosity.

Monolayers of several sterols, cholesterol, cholestanol and the corresponding epi-sterols, also of ergosterol and calciferol, can be built up as multilayers on chromium plates. The thickness per monolayer (16.6 to 17.9 Å.) is about the same as is found by X-ray analysis for 3-dimensional crystals.

Having established these facts for the physical properties of built-up monolayers, the authors studied chemical reactions taking place between molecules in a monolayer with molecules of a surrounding solution and chose as the most suitable example the reaction between digitonin and sterols. It was found that digitonin is adsorbed as a visible film (up to 30 Å. thickness) from a  $10^{-3}$  M solution upon monolayers of cholesterol, cholestanol and ergosterol, but only slightly upon monolayers

of the epi-sterols or calciferol. The specificity of this adsorption parallels the digitonin precipitability of these sterols. Incidentally, the interesting phenomenon of penetration was observed when digitonin from a substrate solution penetrated between sterol molecules in a monolayer on the surface and caused an expansion to about double area even against a pressure of 30 dynes  $\text{cm}^{-1}$ . The epi-sterols give liquid films which expand rapidly, while the normal sterols give very rigid films which expand slowly. These composite (digitonide) monolayers can be transferred as double layers to a prepared plate giving a total thickness of about 60 Å. The films from the epi-sterols are far more unstable than those of the normal sterols and are hydrophobic, while the latter are hydrophilic.

*The Relation of Pathological and Normal Physiology of the Chorda Tympani to the Proper Employment of Thermal Measures in Bell's Palsy.* J. ECHTMAN. M. Rec. 146: 109, August 4, 1937.

In Bell's palsy the following principles are my guide in the application of thermal measures: 1. when the nerve is damaged outside the skull the sense of taste is not affected; 2. when the nerve is involved within the canal the sense of taste is affected (owing to the compression of the corda tympani). Accordingly, I differentiate between two types. In type one, the seat of pathology is the affected cheek. Conventional diathermy is here superior to any other form of heat in all stages. In type two, the seat of pathology is the mastoid region. Here there is pain in most cases, and Reik (quoted by Osler) ascribes it to an acute otitis media (non-suppurative) accompanying the condition. Thermal measures are directed to the mastoid regions: in the early stages infra-red radiation is superior to any other thermal measure, because it has also a definitely favorable effect on the otitis. In the later stages diathermy or short waves are indicated.

*Phenolphthalein as a Dilution Indicator in Gastric Analysis.* F. HOLLANDER, A. PENNER AND M. SALTZMAN. Am. J. Digest. Dis. & Nutrition 4: 364, August 1937.

Phenolphthalein is used as a dilution indicator to determine quantitatively the proportion of residual test meal present in a sample of gastric contents. Two sources of error in its use are demonstrated. (1) The solubility of phenolphthalein is so low that in the course of a Rehfuß determination a considerable amount is lost by precipitation in the stomach. (2) At a pH of 12 (the lowest at which there is a maximum conversion of the indicator to its red salt) phenolphthalein loses color spontaneously. The second of these sources of error can be obviated by alkalinizing the phenolphthalein solution just before the colorimetric determination. The first constitutes a definite contra-indication to the use of phenolphthalein as a dilution indicator. Phenol red is being investigated as a more reliable indicator.

*Excision of Vein for Suppurative Thrombophlebitis.* H. NEUHOF. Ann. Surg. 106: 311, August, 1937.

A suppurative thrombophlebitis of an important neighboring venous trunk exists in all or almost all cases of septicemia derived from a suppurative lesion. Clinically speaking, such a thrombophlebitis is generally either unrecognized or, when suspected, ignored as far as a lead to therapy is concerned. Undoubtedly, spontaneous recovery occurs in some instances of suppurative thrombophlebitis. The chances are, however, that there are many more failures, and, as a result, more fatalities than spontaneous cures. There is advanced, therefore, the argument not only to drain the suppurative lesion but also to determine the presence or absence of a co-existing thrombophlebitis. This is carried out by adequate surgical exposure of the important venous trunk in the region of the suppurative focus. If a thrombophlebitis is

found, the vein is, wherever possible, excised in the attempt to insure eradication of the source of the septicemia. A case report, illustrating the viewpoint expressed in the paper, is presented.

*Determination of the Icteric Index by the Acetone Method.* R. A. NEWBURGER. J. Lab. & Clin. Med. 22: 1192, August 1937.

A simple method is described for the determination of the icteric index, which is a slight modification of that of Ernst and Förster who have introduced the change from the original method of Meulengracht in the use of acetone as a diluent in place of water or saline. Acetone precipitates the proteins and produces a clear filtrate, free of hemoglobin, which permits more accurate estimation of the result. In each specimen of a series of 222 cases, the icteric index by both the water and acetone methods and also the Van den Bergh reaction were determined. An analysis of the results is tabulated and the conclusion is drawn that the acetone method yields results varying within a much narrower range than does the water method, especially where the amount of circulating bilirubin is small. The acetone values are roughly one-third of those obtained by the water method. Values above five by the former technique are regarded as definitely abnormal. Slight elevations are indicative of jaundice, even when unconfirmed by the Van den Bergh reaction, as noted on clinical observations. The method is thought valuable in following the progress of jaundice cases.

*Lymphogranuloma Venereum. Prolonged Derangement of the Serum Lipids and Proteins. Preliminary Report.* I. ROSEN, M.D., H. ROSENFELD, M.D., AND F. KRASNOW, PH.D. Arch. Dermat. & Syphilol. 36: 318, August 1937.

The blood serum of twenty-seven patients with lymphogranuloma venereum was analyzed for total lipids, total cholesterol, cholesterol-esters, free cholesterol, lipid phosphorus (lecithin), albumin, and globulin. All patients presented clinical manifestations of the disease and positive Frei tests. The duration of the disease varied between three weeks and seventeen years.

The lipid content (total cholesterol, cholesterol-esters) and the albumin in the serum were significantly below the normal, the free cholesterol above the normal, esters correspondingly decreased. In 100 per cent of the cases the globulin was increased to between 2.4 and 6.68 mg. per cent. The highest increase of globulin was found in cases with rectal stricture and esthiomene (the late stage of this disease).

Since the positive Frei test indicates only the fact that the patient once had an infection of lymphogranuloma venereum and stays positive for the whole life, the changes in the blood serum seem to indicate progression of the disease because the biochemical changes were apparently more accentuated in cases of longer duration.

Further investigations are under way.

*Chest Lead Tracings in Arterial Hypertension with Cardiac Enlargement.* I. R. ROTH. Am. Heart J. 14: 155, August 1937.

An electrocardiographic pattern of the apical chest lead tracing in certain cases of arterial hypertension with cardiac enlargement is presented. The ventricular complex in this tracing is characterized by a QRS which consists predominantly of a large negative component and by an upright T-wave. The pattern is essentially a modified standard Lead III, and is due, apparently, to the axillary situation of the exploring electrode.

The left pectoral chest lead tracing is not appreciably altered in these cases, and, therefore, stands out in marked contrast to the apical lead. This lead may serve in problems of differential diagnosis. In fact, the left pectoral lead is the chest lead of

choice and the so-called apical lead should be avoided as a routine lead in cases of arterial hypertension with left heart enlargement.

*Prognostic Factors in Spontaneous Subarachnoid Hemorrhage.* I. STRAUSS AND S. TARACHOW. Arch. Neurol. & Psychiat., 38: 239, August 1937.

One hundred and five cases of spontaneous subarachnoid hemorrhage were studied. The syndrome was viewed as symptomatic of a variety of pathologic states, the prognosis varying with that of the underlying or associated disease process. An effort was made to study the incidence of systemic or local disease. Spontaneous subarachnoid hemorrhage may be symptomatic of cardiorenal vascular disease, tumor of the brain, subacute bacterial endocarditis, purpura, polycythemia, Hodgkin's disease or myeloid leukemia. It may be associated with cerebrospinal syphilis, tuberculosis, diabetes, epilepsy or acute glomerulonephritis, or there may be no clinically discoverable disease. In the only four cases in which the hemorrhage was associated with clinically definite cerebrospinal syphilis, the patients died. The prognosis tends to be worse with the presence of generalized vascular disease and better in the absence of clinically discoverable disease. In the absence of clinically discoverable disease the prognosis becomes worse, the older the patient. In the absence of generalized disease, a history of proved or presumed previous attacks tends to make the prognosis better. This history is usually found in young persons and suggests congenital aneurysm or aneurysm with cerebral arteriosclerosis in young persons. The average duration between the observed attack and the next expected attack is two years and six months. Presumptive recurrences occur, even though not proved by examination of the spinal fluid.

*An Instrument for the Continuous Reading of Rectal Temperature.* W. BIERMAN. J.A.M.A. 109: 887, September 11, 1937.

A thermometer is described which permits continuous reading of rectal temperature during the administration of physically induced fever. The instrument is thirteen and one-half inches long and three-eighths of an inch in diameter. The last four inches are flattened to a width of five-eighths of an inch. Etched lines indicate temperature in fifths of a degree F. from 98 to 112°F. Prisms magnify the mercury column so that it can be read at a distance. Two inches from the tip is a small bulb which facilitates retention of the instrument. A special housing protects the thermometer from breakage. The protruding portion rests on a pillow to keep it in place.

*Prolonged Survival following Cholecystogastrostomy for Obstructive Jaundice Due to Carcinoma of the Head of the Pancreas.* G. D. OPPENHEIMER. Ann. Surg. 106: 461, September 1937.

This is a case report of a 60 year old male who died twenty-nine months following a cholecystogastrostomy for obstructive jaundice. The post mortem examination confirmed the operative diagnosis of carcinoma of the head of the pancreas. There were no metastases.

Roentgenologic examination following a barium meal showed air in the biliary system on one occasion and barium in the common and hepatic ducts at a later examination. However, ascending infection did not occur since there were no microscopic evidences of cholangitis or hepatitis. The value of the operative procedure as a palliative measure in this particular instance was evident.

*Electrolytes of Blood and Urine of Dogs with Acute Hepatic Injury Produced by Arsenamine.* L. J. SOFFER, D. A. DANTES AND H. SOBOTKA. Arch. Int. Med. 60: 509, September 1937.



Studies are reported of electrolytes of blood and urine in dogs with acute diffuse parenchymal damage of the liver produced by the intravenous injection of arsphenamine.

The most striking changes observed were pronounced hemoconcentration and acidosis, a fall in the blood chloride and an increase in the inorganic phosphate and especially lactic acid of the serum. In some dogs, severe hypoglycemia developed.

While the two latter changes are the result of hepatic injury, leading to failure of glycogen formation from lactic acid, the hyperphosphatemia probably represents a manifestation of failing renal function. The mechanism of the hypochloremia is not clear.

Other less constant electrolytic changes were a slight drop in the blood sodium and a considerable increase in potassium. The serum calcium remained unchanged in all animals.

There occurred a marked polyuria and with it an increase in the lactic acid and total protein excretion in the urine, and a great reduction in the excretion of chloride and inorganic phosphate.

*The Disclosure of Foster-Parentage to a Boy. Behavior Disorders and Other Psychological Problems Resulting.* S. TARACHOW. Am J. Psychiat., 94: 401, September 1937.

The problem of the disclosure of foster parentage is discussed. The case material is taken from a series of boys admitted to The New York State Training School for Boys. The boys were usually illegitimate children adopted in early childhood by foster parents. At about puberty the truth would be somehow revealed. These boys showed a good deal of preliminary doubt concerning their parentage, and various fantasies concerning their real parents, especially dealing with atonement and forgiveness. The boys developed resentment to their foster parents and characteristically began to run away from home or show more widespread antisocial symptoms. Perhaps the most pernicious result in the mind of the child was the resulting ambivalent attitude to the foster parents, love for the past security and hate for the withdrawal of that relationship.

*Torsion of the Pedicle In Ovarian Tumors.* P. BERNSTEIN. Arch. Surg. 35: 787, October, 1937.

This paper describes ninety-seven cases of torsion of the pedicle in ovarian tumors, which were found among 1,101 ovarian tumor operations at The Mount Sinai Hospital (between the years of 1924 and 1925).

Resume of literature on the subject is presented, as well as statistical comparisons among the various types of ovarian cysts. A discussion regarding cause, extent and direction of torsion is briefly presented. The relationship between rotation and the size of the tumor is derived from this study. The relative frequency of different ovarian tumors in given locations is compared with the incidence of ovarian twisting in these locations.

Symptoms, pathological changes and complications incident to rotation phenomena are presented. The bearing upon the menstrual function is also discussed.

## NEWS AND NOTES

### POST-GRADUATE MEDICAL COURSES TO BE OFFERED AT THE MOUNT SINAI HOSPITAL

#### FIRST SERIES

The following courses will be conducted from the week of November 6th through the week of December 25th, 1939, unless otherwise specified.

#### BACTERIOLOGY

*Medicine Ce19*—Clinical bacteriology and immunology. Fee \$30. Dr. SHWARTZMAN.  
Two hours a week. (Hours to be arranged.)

*Medicine Ce20*—Practical course in clinical bacteriology. Fee \$25. Miss HERSCHBERGER.

Two hours a week. (Hours to be arranged.)

#### CHEMISTRY

*Chemistry Ce1*—Pathological chemistry. Fee \$30. Dr. SOBOTKA.

One hour, once a week. (Hours to be arranged.)

*Chemistry Ce2*—Routine chemical methods as used at The Mount Sinai Hospital.  
Fee \$35. Miss REINER.

2-4 p.m., one afternoon a week. (Hours to be arranged.)

#### GASTROENTEROLOGY

*Medicine Ce31*—Diagnosis and treatment of diseases affecting the gastrointestinal tract. Fee \$50. Drs. CROHN, WINKELSTEIN, GRANET and YARNIS.

9:30-11:30 a.m., Monday, Wednesday and Friday; 3-5 p.m., Thursday.

#### GYNECOLOGY

*Gynecology Ce1a*—Gynecological diagnosis, treatment and pathology (Dr. Geist's Service). Fee \$60. Drs. GEIST, MAYER, SALMON, GAINES and MINTZ.

Daily a.m. and p.m. except Saturday p.m.

*Gynecology Ce1b*—Clinical course in gynecology together with a survey of gynecological pathology. (Dr. Rubin's Service.) Fee \$60. Drs. RUBIN, GOLDBERGER, BERNSTEIN, WIMPFHEIMER and KLEMPNER.

Daily a.m. and p.m. except Saturday p.m.

#### MEDICINE (GENERAL)

*Medicine Ce2*—A course in diagnosis and therapy. Fee \$35. Drs. B. S. OPPENHEIMER, MOSCHCOWITZ, OTTENBERG, BECK and Staff of Second Medical Service.

3-5 p.m., Monday and Thursday.

November 6, 1939-January 11, 1940.

*Medicine Ce3*—Diseases of the kidneys and arteries. Fee \$15. Dr. MOSCHCOWITZ.  
4-5 p.m., Thursday.

December 21, 1939-February 8, 1940.

*Medicine Ce4*—Diseases of the liver and biliary passages. Fee \$50. Drs. GARLOCK, KLEMPERER, LICHTMAN, OTTENBERG and SOBOTKA.

1:30-3:30 p.m., Wednesday. There will be three additional sessions in Pathology, and three additional sessions in Chemistry on Fridays, 1-3 p.m.

November 8, 1939-January 17, 1940.

*Medicine Ce5*—General bedside therapy. Fee \$30. Dr. POLL.

3:30-4:30 p.m., Monday, Wednesday and Friday.

*Medicine Ce6*—Clinical manifestations of coronary artery disease. Fee \$25. Drs. BOAS and LEVY.

3-5 p.m., Monday.

November 6, 1939-January 8, 1940.

*Medicine Ce8*—Practical hematology. Fee \$35. Dr. ROSENTHAL.

2-4 p.m., Monday and Thursday.

*Medicine Ce9*—Clinical electrocardiography. Fee \$35. Drs. MASTER, JAFFE and DACK.

1-3 p.m., Friday.

November 10, 1939-January 12, 1940.

*Medicine Ce12*—Heart diseases in adults. Fee \$40. Drs. I. R. ROTH and AVERBUCK.  
10 a.m.-12 m., Monday.

November 6, 1939-January 22, 1940.

*Medicine Ce13*—Allergy in relation to internal medicine. Drs. HARKAVY, ABRAMSON and ROMANOFF.

(a) 9:30-11:30 a.m., Monday, Wednesday and Friday.

(b) 2:30-4:30 p.m., Monday.

Courses (a) and (b) are complementary, and may or may not be taken together.

(a) Fee \$35, if taken alone.

(b) Fee \$25, if taken alone.

(a) and (b), if taken combined, fee will be \$50.

*Medicine Ce15*—Practical course in peripheral vascular disorders. Fee \$25. Dr. SILBERT.

9:30-11 a.m., Thursday.

November 9, 1939-January 25, 1940.

*Medicine Ce16*—Correlation of the electrocardiogram with the fluoroscopy and x-ray of the heart. Fee \$40. Drs. MASTER, DACK and JAFFE.

10 a.m.-12 m., Friday.

November 10, 1939-January 26, 1940.

*Medicine Ce21*—Diagnostic or medical proctology. Fee \$35. Drs. CROHN and WINKELSTEIN.

One session of two hours each week, probably in the morning.

## NEUROLOGY

*Neurology Ce1*—Advanced course in clinical neurology. Fee \$100. Drs. WECHSLER, IRA COHEN, GLOBUS, BRICKNER and Staff.

One hour, twice weekly. Either October, 1939-January 31, 1940 or February, 1940-May 31, 1940.

*Neurology Ce2*—Applied neuroanatomy and neuropathology. Fee for entire course, \$100. Dr. GLOBUS.

(a) Neuroanatomy I. Fee \$30.

(b) Neuroanatomy II. Fee \$30.

(c) Neuropathology I. General. Fee \$30.

(d) Neuropathology II. Special. Fee \$30.

Hours to be arranged.

This course may be taken in combination with Neurology Ce1 at a fee of \$150.

*Neurology Ce3*—Neurological, neuropsychiatric and neurosurgical clinics. Fee \$20.  
 Dr. WECHSLER and Staff.  
 2:15-3:15 p.m., Wednesday.  
 November, 1939, through April, 1940.

### OPHTHALMOLOGY

(The hours of these courses are subject to change to meet the convenience of instructor and student.)

*Ophthalmology Ce1*—Ophthalmoscopy. Fee \$50. Dr. SCHLIVEK.

3-4 p.m., Monday and Thursday.

November 6-December 14, 1939.

*Ophthalmology Ce2*—Ophthalmic surgery. Fee \$75. Dr. MINSKY.

4-6 p.m., Monday and Thursday, and other hours as operations and material permit.

November 6-December 14, 1939.

*Note: Open to ophthalmologists only.*

*Ophthalmology Ce3*—Slit lamp microscopy of the living eye. Fee \$35. Dr. LAMBERT.

3-4 p.m., Thursday.

*Ophthalmology Ce4*—(a) Refraction and (b) muscles. Dr. LAVAL.

(a) Refraction: 2-4 p.m., Monday. Fee \$45, alone.

(b) Muscles: 3-4 p.m., Wednesday. Fee \$25, alone.

If taken combined, fee will be \$60.

*Ophthalmology Ce5*—Histopathology of the eye. Fee \$75. Drs. WEXLER and LAVAL.

8-10 p.m., Friday.

October 13-December 22, 1939.

*Ophthalmology Ce6*—External diseases of the eye. Fee \$35. Dr. WEXLER.

2-4 p.m., Friday.

*Ophthalmology Ce7*—Embryology of the eye. Fee \$35. Dr. KORNZWEIG.

3-5 p.m., Wednesday.

*Ophthalmology Ce8*—Ophthalmic neurology. Fee \$35. Dr. LAST.

4-6 p.m., Tuesday.

*Ophthalmology Ce9*—Physiological optics. Fee \$25. Dr. MILLER.

A six weeks' course, two hours a week. Hours to be arranged.

For course in Neuro-ophthalmology, please see Neurology Ce4. (Page 167)

### ORTHOPEDICS

*Orthopedics Ce1*—Practical course in injuries and diseases of the bones and joints.

Fee \$25. Drs. SELIG, LIPPMANN, BICK and SCHEIN.

3-4 p.m., Monday and Thursday.

### OTOLOGY

*Otology Ce3*—Otologic histopathology. Fee \$35. Dr. DRUSS.

4-6 p.m., Tuesday and Friday.

November 7-December 8, 1939.

### PEDIATRICS

*Diseases of Children Ce1*—Clinical pediatrics: A comprehensive course in diseases of children. Fee \$35. Dr. SCHICK and the Pediatric Staff.

3-5 p.m., Tuesday and Thursday.



*Diseases of Children Ce2*—Nutrition of infants and older children. Disorders of nutrition. Fee \$25. Dr. SCHICK.

3-4 p.m., Tuesday and Thursday.

*Diseases of Children Ce3*—Heart disease in children. Fee \$35. Drs. ROTH, LEADER and NEWMAN.

9:30 a.m.-12 m., Saturday.

*Diseases of Children Ce4*—Conduct disorders of children. Fee \$25. Dr. WILE.

2-4 p.m., Wednesday. Eight lectures and eight clinics.

*Diseases of Children Ce5*—Asthma in children. Fee \$25. Dr. PESHKIN.

3:30-5:30 p.m., Friday.

*Diseases of Children Ce6*—Diabetes mellitus in children. Fee \$35. Dr. FISCHER.

9-10:30 a.m., Saturday, Clinic in the Out-patient Department.

Lectures: Time to be arranged.

November 11-December 2, 1939.

### PHYSICAL THERAPY

*Physical Therapy Ce1*—Physical therapy for the general practitioner. Fee \$50.

Drs. BIERMAN, LICHT and KOLIN.

9:30-11:00 a.m., Tuesday and Thursday.

### PROCTOLOGY

*Surgery Ce1*—Intensive course in proctology. Fee \$50. Drs. MANHEIM, GARLOCK, GOLDSCHMIDT and PESKIN.

9:30-11:30 a.m., Wednesday and Friday.

*Note: Limited to physicians who have had either surgical training or a houseship in surgery.*

### SECOND SERIES

The following courses will be conducted from the week of February 5th through the week of March 25th, 1940, unless otherwise specified.

### DERMATOLOGY

*Dermatology Ce1*—Dermatology and syphilis. Fee \$35. Drs. I. ROSEN, CHARGIN, PECK and Staff.

2-4 p.m., Tuesday, Thursday and Saturday.

*Dermatology Ce2*—Clinical dermatology. Fee \$35. Drs. I. ROSEN, LEVIN and SCHEER.

2-3 p.m., Monday, Wednesday and Friday. Out-patient Department and wards.

### ENDOCRINOLOGY

*Endocrinology Ce1*—Gynecological endocrinology. Laboratory course in bioassay of gonadotropic and female and male sex hormones. Fee \$50. Drs. FRANK, GOLDBERGER, FELSHIN and KLEMPNER.

2-4 p.m., Tuesday and Friday.

February 6-March 3, 1940.

### INTENSIVE GASTROENTEROLOGY

*Medicine Ce32*—Intensive four weeks' course in gastroenterology: Its relation to internal medicine and abdominal surgery. Fee \$100. Drs. CROHN and WINKELSTEIN, *Gastroenterology*; Dr. KLEMPERER, *Pathology*; Dr. GOLDFARB, *Radiology*; Drs. BAEHR, and OTTENBERG, *Internal Medicine*; Drs. COLP and

GARLOCK, *Surgery*; Drs. HOLLANDER and DOUBILET, *Physiology*; Dr. KRAMER, *Gastroscopy*; Dr. MANHEIM, *Proctology*; Dr. GRANET, *Laboratory Procedures*; Dr. YARNIS, *Sigmoidoscopy*.

9 a.m.-5 p.m., Monday through Saturday. (Probably during the month of May, 1940.)

*Note: This course will be given if the minimal number of students register. Application for admission must be made before April 15th.*

#### GYNECOLOGY

*Gynecology Ce2*—Gynecological pathology. Fee \$60. Drs. GEIST, GAINES and WALTER.

2-4 p.m., Tuesday and Friday.

April 2-May 10, 1940.

#### LARYNGOLOGY

*Laryngology Ce1*—Histologic anatomy and pathology of the upper respiratory tract. Fee \$50. Drs. KLEMPERER, OTANI and SOM.

Twenty-five hours, each session 1½ hours. (Hours to be arranged, starting the week of February 5th.)

#### MEDICINE (GENERAL)

*Medicine Ce1*—Diseases of metabolism and practical dietetics. Fee \$35. Drs. BAEHR, LANDE, POLLACK, SOFFER and ADLERSBERG and Dietetic Staff.

2-3:30 p.m., Monday, Wednesday and Friday.

*Medicine Ce7*—Practical pharmacology. Fee \$25. Dr. H. T. HYMAN.

2-3 p.m., Tuesday and Friday.

*Medicine Ce9*—E.C.—Clinical electrocardiography. Fee \$35. Drs. MASTER, JAFFE and DACK.

1-3 p.m., Friday.

February 9-April 12, 1940.

*Medicine Ce10*—Diseases of the heart: Clinical features interpreted through roentgenologic, anatomic and histologic findings. Fee \$50. Drs. B. S. OPPENHEIMER, MASTER, FRIEDBERG, KLEMPERER, JAFFE, DACK and HORN.

10 a.m.-12 m., probably Friday.

February 9-April 19, 1940.

*Medicine Ce11*—Clinical electrocardiography. Advanced course. Fee \$35.

Drs. MASTER, JAFFE and DACK.

1-3 p.m., Monday.

February 5-April 1, 1940.

*Medicine Ce14*—Advanced course in diseases of the chest. Fee \$35. Members of the Chest Group: Drs. NEUHOF, RABIN, TOUROFF, HENNEL and SCHAPIRO.

9-11 a.m., Friday.

February 9-May 24, 1940.

#### INTENSIVE CARDIOLOGY

*Medicine Ce30*—Intensive four weeks' course in cardiology. Fee \$100. Drs. B. S. OPPENHEIMER, M. H. BASS, E. P. BOAS, A. M. FISHBERG, A. M. MASTER, M. L. SUSSMAN, I. R. ROTH, S. H. AVERBUCK, C. K. FRIEDBERG, S. SILVER, H. MANN, S. DACK, H. L. JAFFE, and H. HORN.

9 a.m.-5 p.m., Monday through Saturday. (Probably during the month of May, 1940.)

## NEUROLOGY

The courses in Neurology, namely, Neurology Ce1 and Ce2, will also be offered, starting the week of February 5, 1940.

*Neurology Ce4*—Advanced course in neuro-ophthalmology. Fee \$50. Drs. BENDER and SAVITSKY.

Two-hour session, twice a week. Hours to be arranged.

## OPHTHALMOLOGY

*Ophthalmology Ce10*—Systematic eye examination and functional testing. Fee \$35.

Dr. MINSKY.

3-5 p.m., Wednesday.

*Note: Open to ophthalmologists only.*

## OTOLOGY

*Otology Ce2*—Otologic neurology. Fee \$25. Dr. MAYBAUM and Staff.

2-3 p.m., Friday.

February 9-March 1, 1940.

## PATHOLOGY

*Medicine Ce17*—General and special pathology. Fee \$40. Drs. KLEMPERER and OTANI.

Thirty hours. (Hours to be arranged.)

*Medicine Ce18*—Surgical pathology. Fee \$40. Drs. KLEMPERER and OTANI.

Thirty hours. (Hours to be arranged.)

*Note: This course is given at the conclusion of Medicine Ce17. However, Medicine Ce17 is not a prerequisite for Medicine Ce18.*

## PEDIATRICS

*Diseases of Children Ce1*—E.C.—Clinical pediatrics: A comprehensive course in diseases of children. Fee \$35. Dr. SCHICK and the Pediatric Staff.

*Diseases of Children Ce4*—E.C.—Clinical measurements of intelligence. Fee \$15.

Dr. WILE.

2-3 p.m., Wednesday.

## RADIOLOGY

The following courses in Clinical Roentgenology will be offered during October, November and December, 1939, and will be repeated during January, February and March, 1940:

*RC2*—Roentgenology of the osseous system. Dr. MARCY L. SUSSMAN.

*RC9*—Roentgenology of the thorax. Dr. MARCY L. SUSSMAN.

*RC10*—Roentgenology of the heart and mediastinum. Dr. MARCY L. SUSSMAN.

*RC11 and 12*—Roentgenology of the gastro-intestinal tract. Drs. S. J. GOLDFARB and MARCY L. SUSSMAN.

*RC17*—Roentgenology of the genito-urinary tract. Dr. MARCY L. SUSSMAN.

*RC18*—Gross pathology for radiologists. Dr. PAUL KLEMPERER.

The following courses in Radiotherapy will be offered during April, May and June, 1940:

*RT*—Principles of radiation therapy. Dr. WILLIAM HARRIS.

*RT-2*—Microscopic tumor pathology. Dr. PAUL KLEMPERER.

*RT-2*—General principles of skin, intra-oral disease, lower respiratory system, breast, circulatory system and blood-forming organs, bone tumors. Breast neoplasms. Dr. WILLIAM HARRIS.

*RT-2*—General principles, head and neck, gastro-intestinal and genito-urinary tracts. Drs. WILLIAM HARRIS, M. GOLAN and S. RICHMAN.

*RT-2*—Blood dyscrasias, lymphosarcoma infections, etc. Drs. WILLIAM HARRIS, A. KEAN and N. ROSENTHAL.

*RT-2*—Gynecology. Dr. WILLIAM HARRIS.

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The courses in Radiology are subject to change.

For further information regarding courses in Radiology apply to the Dean of the School of Medicine, Columbia University, 630 West 168th Street, New York City.

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For further information for all courses, with the exception of those in Radiology, please apply to Miss Edith L. Levy, Secretary for Medical Instruction, The Mount Sinai Hospital, New York City.



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## THE EDWARD GAMALIEL JANEWAY LECTURE

SOME BIOLOGICAL ASPECTS OF PROTEIN CHEMISTRY<sup>1</sup>

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The major part of the organic substance of the human and the animal body consists of proteins. To the proteins belong substances serving rather different biological functions, such as: hair and nails; muscle and skin tissue; tendons; egg white; the casein of milk; the fiber of natural silk; the red substance of blood; the digestive enzymes pepsin and trypsin; the hormone insulin; certain viruses. The proteins of one animal or plant species differ from those of all other species. Wherever life phenomena occur, proteins are involved in one way or another. Proteins are therefore regarded as being the chemical requisite of life. What particular chemical property qualifies the proteins for their unparalleled biological significance has hitherto been unknown. Due to their extremely complicated chemical nature, the proteins have resisted a detailed exploration by means of the established methods. Therefore, the proteins are usually subdivided on the basis of solubility properties, salting out effects, coagulation phenomena, and similar criteria. There can be little doubt, however, that the singular biological rôle of proteins must have a basis in common structural attributes of the various proteins. It is likewise to be expected that the physiological and serological differences between various proteins will eventually be explained by differences in the composition and the pattern of these proteins. The ultimate goal of protein chemistry is, therefore, to establish the molecular composition and the architecture of the various proteins with the same precision as the molecular composition and the architecture of simpler molecules have been ascertained.

The investigation of simple organic compounds starts with an estimation, by elementary analysis, of the nature and the number of atoms that constitute the molecule. In a protein molecule the number of carbon, hydrogen, nitrogen, and oxygen atoms is so immense—a protein molecule may consist of ten thousands of atoms—that the elementary analysis cannot reveal their exact number and ratio. Here an indirect procedure is necessary, based on the following facts. On hydrolysis the proteins are split into a number of amino acids, each of which contains relatively few atoms. Therefore we regard the molecule of a protein as containing a number of

<sup>1</sup> Delivered at the Blumenthal Auditorium, The Mount Sinai Hospital, New York City, May 16, 1939.

smaller units which we call amino acid residues (table I). This may also be expressed as follows. In a protein molecule the atoms are grouped into units of a higher order—the amino acid residues—and these, in turn, are combined to form the protein molecule. Since the constitution of the amino acid residues is well known, the question of the composition of a protein molecule is, at the present time, reduced to the estimation of the nature and the number of the amino acid residues that constitute the protein molecule. The amino acid residues play the same rôle with respect to the quantitative composition of a protein molecule as do the atoms with respect to simple organic molecules. The main difficulty in performing a constituent analysis of a protein results from the fact that each protein yields a mixture of about 20 to 25 amino acids and that these amino acids exhibit rather similar physical and chemical properties. The task is to determine with the utmost accuracy every single constituent of

TABLE I

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<i>General formula of an amino acid</i>	
$\begin{array}{c} \text{R} \\   \\ \text{NH}_2 \cdot \text{CH} \cdot \text{COOH} \end{array}$	
<i>General formula of proteins (E. Fischer)</i>	
$\begin{array}{ccccccc} \text{R} & & \text{R} & & \text{R} & & \text{R} & & \text{R} \\   & &   & &   & &   & &   \\ \text{NH}_2 \cdot \text{CH} \cdot \text{CO} - \text{NH} \cdot \text{CH} \cdot \text{CO} - \text{NH} \cdot \text{CH} \cdot \text{CO} \cdots \cdots \text{NH} \cdot \text{CH} \cdot \text{CO} - \text{NH} \cdot \text{CH} \cdot \text{COOH} \end{array}$	
(R = Side chains)	

---

so complex and unpleasant a mixture. For the separation from each other of the various amino acids in a protein hydrolysate many procedures have been developed during the past forty years. These methods belong to the most ingenious and also the most difficult of analytical operations. I need only mention such names as Dakin, Van Slyke, Osborne, and Vickery in order to recall to your mind the achievements of protein analysis in this country during the last decades. I should like to demonstrate the best constituent analyses of several proteins obtained by the classical methods (table II). Such analyses established beyond any doubt the fact that the various proteins show wide differences in their amino acid content. Thus, for example, egg albumin seemed to give no glycine at all; gelatin yielded more than 25 per cent; and silk fibroin not less than 40.5 per cent. The fact that the analytical figures revealed no arithmetical regularity whatsoever has always been taken to indicate an extremely complicated structure for the proteins, the intricacy of which was regarded as exceeding human understanding.



One should not, however, overlook the fact that the values obtained by the classical methods of protein analysis can be regarded only as approximations and that in many instances they include experimental errors of between 10 and 50 per cent. Constituent analyses obtained by these methods cannot properly represent protein structure and may even exaggerate its complexity. It seemed possible, therefore, to simplify the picture of protein composition by improving the methods for determining the amino acids. In order to test this possibility a new kind of analysis was recently developed in collaboration with Doctors Niemann, Stein and

TABLE II

*The amino acid content of gelatin, casein, egg albumin, and silk fibroin (Mitchell and Hamilton)\**

	GELATIN	CASEIN	EGG ALBUMIN	SILK FIBROIN
Glycine.....	25.5	0.4	0.0	40.5
Alanine.....	8.7	1.8	2.2	25.0
Valine.....	0.0	7.9	2.5	
Leucine-isoleucine.....	7.1	9.7	10.7	2.5
Aspartic acid.....	3.4	4.1	6.2	
Glutamic acid.....	5.8	21.8	13.3	
Hydroxyglutamic acid.....	0.0	10.5		
Serine.....	0.4	0.5		1.8
Proline.....	9.5	8.0	3.6	1.0
Hydroxyproline.....	14.1	0.2		
Phenylalanine.....	1.4	3.9	5.1	1.5
Tyrosine.....	0.3	6.5	4.0	11.0
Cystine.....	0.2	0.3	0.9	
Arginine.....	9.1	5.2	6.0	
Histidine.....	0.9	2.6	2.3	
Lysine.....	5.9	7.6	3.8	
Tryptophane.....	0.0	2.2	1.3	
Total.....	92.3	93.2	61.9	83.3

\* Mitchell and Hamilton, *The Biochemistry of the Amino Acids*, New York, 1929, American Chemical Society Monograph Series, The Chemical Catalog Co., Inc.

Ing (1, 2, 3). With this method the precision of protein analysis was improved to such a degree that the composition of a protein can now be determined with an accuracy approaching that of an elementary analysis. By a combination of several of the previously known methods and of those worked out in our laboratory, it was possible to carry out constituent analyses of several proteins. What results have been obtained and how they may be interpreted may now be illustrated by the example of ox fibrin and of several other proteins (4, 5, 6). The determination of several constituents of cattle blood fibrin by the improved analytical methods reveals the percentages of each of these constituents, as reported in Column 1 of

table III. From the percentage values there may be calculated: (1) the ratios in which the single constituents are present; (2) the total number of constituents per molecule of fibrin; (3) the fraction of the total number that each constituent comprises.

I need not discuss these calculations in detail, but should like to mention several of the rather startling results.

We find, for instance, that one molecule of fibrin contains 576 amino acid residues; that exactly  $\frac{1}{8}$  of the total number of these residues are glutamic acid residues; and that lysine comprises  $\frac{1}{12}$ , arginine  $\frac{1}{18}$ , aspartic acid  $\frac{1}{18}$ , proline  $\frac{1}{18}$ , and so forth. Arginine, aspartic acid, and proline—

TABLE III  
*Ratio of amino acids in cattle blood fibrin*

AMINO ACID	WEIGHT	MOL. WT.	GM.-MOLECULES PER 100 GM. PROTEIN	RATIO	FRACTION OF TOTAL RESIDUES
	(1)	(2)	(3)	(4)	(5)
	<i>per cent</i>				
Glutamic acid .....	14.1	147	0.095 <sub>9</sub>	72	8
Lysine.....	10.1	146	0.069 <sub>1</sub>	48	12
Arginine.....	7.7	174	0.044 <sub>2</sub>	32	18
Aspartic acid.....	5.9	133	0.044 <sub>3</sub>	32	18
Proline.....	5.1	115	0.044 <sub>3</sub>	32	18
Tryptophane.....	5.0	204	0.024 <sub>5</sub>	18	32
Histidine.....	2.5	155	0.016 <sub>1</sub>	12	48
Methionine.....	2.6	149	0.017 <sub>4</sub>	12	48
Cysteine.....	1.5	240	0.006 <sub>2</sub>	9	64

Average residue weight of amino acids in cattle fibrin is 120.3.

100 gm. of fibrin must give on hydrolysis  $100/120.3 = 0.831$  gm.-molecules of an average amino acid.

Lysine comprises  $0.0691/0.831 = 1/12$  of all the constituent amino acids.

Cattle fibrin must contain  $72 \times 8 = 576$  amino acid residues of an average weight of 120.3. Cattle fibrin, therefore, has a molecular weight of  $576 \times 120.3 = 69,300$ .

as well as histidine and methionine—are present within the fibrin molecule in sharply equivalent amounts. It seems that the fibrin molecule is no longer to be regarded as an accumulation of amino acid residues without any rule and regularity. On the contrary, I should like to direct your attention to the fact that the total number of residues present in one molecule of fibrin, namely, 576, can be expressed as powers of 2 and 3—that is, as  $2^6 \times 3^2$ . And all the figures indicating the number of accurately determined amino acid residues and their fractional amount in respect to the total number present in the fibrin molecule can also be presented as powers of 2 and 3.

These numerical rules are not restricted solely to fibrin. In order to demonstrate their validity for three other proteins, table IV reports the

ratios and fractional values for a number of constituents of ox hemoglobin, chicken egg albumin, and silk fibroin. The experimental results reported in tables III and IV may be expressed by the general formulas shown in table V. These formulas set forth the fact that the composition of hemoglobin, fibrin, egg albumin, and silk fibroin is such that the total number of amino acid residues in the protein molecule is  $2^n \times 3^m$ , where  $n$  and  $m$  are whole numbers; and the number of any individual amino acid residues

TABLE IV

*Ratios (R) and reciprocal fractional values (F) of cattle globin, cattle fibrin, chicken egg albumin, and silk fibroin*

AMINO ACID RESIDUE	CATTLE GLOBIN		CATTLE FIBRIN		CHICKEN EGG ALBUMIN		SILK FIBROIN	
	R	F	R	F	R	F	R	F
All residues.....	$2^5 \times 3^2$		$2^5 \times 3^2$		$2^5 \times 3^2$		$2^5 \times 3^4$	
Arginine.....	$2^2 \times 3^1$	$2^4 \times 3^1$	$2^5 \times 3^0$	$2^1 \times 3^2$	$2^2 \times 3^1$	$2^3 \times 3^1$	$2^2 \times 3^1$	$2^3 \times 3^3$
Lysine.....	$2^2 \times 3^2$	$2^4 \times 3^0$	$2^4 \times 3^1$	$2^2 \times 3^1$	$2^2 \times 3^1$	$2^3 \times 3^1$	$2^2 \times 3^0$	$2^3 \times 3^4$
Histidine.....	$2^5 \times 3^0$	$2^1 \times 3^2$	$2^2 \times 3^1$	$2^4 \times 3^1$	$2^2 \times 3^0$	$2^3 \times 3^2$	$2^0 \times 3^0$	$2^5 \times 3^4$
Aspartic acid.....	$2^5 \times 3^0$	$2^1 \times 3^2$	$2^5 \times 3^0$	$2^1 \times 3^2$	$2^4 \times 3^0$	$2^1 \times 3^2$		
Glutamic acid.....	$2^4 \times 3^0$	$2^2 \times 3^2$	$2^3 \times 3^2$	$2^3 \times 3^0$	$2^2 \times 3^2$	$2^3 \times 3^0$		
Glycine.....							$2^4 \times 3^4$	$2^1 \times 3^0$
Alanine.....							$2^3 \times 3^4$	$2^2 \times 3^0$
Tyrosine.....	$2^2 \times 3^1$	$2^4 \times 3^1$			$2^3 \times 3^0$	$2^2 \times 3^2$	$2^1 \times 3^4$	$2^4 \times 3^0$
Proline.....	$2^2 \times 3^1$	$2^4 \times 3^1$	$2^5 \times 3^0$	$2^1 \times 3^2$				
Tryptophane.....			$2^1 \times 3^2$	$2^5 \times 3^0$				
Cysteine.....	$2^0 \times 3^1$	$2^6 \times 3^1$	$2^0 \times 3^2$	$2^6 \times 3^0$	$2^2 \times 3^0$	$2^3 \times 3^2$		
Methionine.....			$2^2 \times 3^1$	$2^4 \times 3^1$	$2^2 \times 3^1$	$2^3 \times 3^1$		

TABLE V

*General formulas for egg albumin, cattle globin, cattle fibrin, and silk fibroin*

(1) Total number of residues	$N_t = 2^m \times 3^n$
(2) Number of an individual residue	$N_i = 2^{m'} \times 3^{n'}$
(3) Reciprocal fractional value of an individual residue	$F_i = 2^{m''} \times 3^{n''}$
	$m = m' + m''$
	$n = n' + n''$

$n$  and  $m$  are positive whole numbers.

$m'$ ,  $n'$ ,  $m''$ ,  $n''$  are either zero or positive whole numbers.

in the protein molecule is  $2^{n'} \times 3^{m'}$ , where  $n'$  and  $m'$  may be either 0 or a whole number.

The experimental values on which our general formulas are based had been obtained before the latest improvements of the constituent analysis of proteins were completed in all details. A few minor corrections may therefore become necessary. However, the general fact will remain unaltered that proteins have in common a general architecture reflected in

precise numerical rules which are not found for any other group of biological compounds. I may add that these numerical rules are exhibited not only by fibrin, globin, fibroin, and egg albumin, but also by proteins so different in nature as are skin and bone collagen, elastin (7), insulin (8), and the protein of the yellow enzyme of Warburg (9). It follows that living organisms apparently synthesize only proteins that exhibit these numerical rules.

In this connection I should like to mention the well-known findings of Svedberg (10) and others, that a great number of proteins, when investigated in the ultracentrifuge, exhibit particle sizes that are approximately whole number multiples of 17,500, where the figure 2 is taken as the particle size of the hydrogen molecule. The regularity of the protein particle sizes has been interpreted as pointing to a common plan for the architecture of the protein molecule. As the basis of this common plan we regard our finding that various proteins fall into classes containing a definite number of amino acid units: for example, hemoglobin and fibrin fall into the class with 576 units, silk fibroin into the class with 2,592 units, and so forth.

My discourse up to this point may have indicated that the molecule of a protein is a definite entity just as is the molecule of a simpler compound and that, in the future, it may become possible to determine the composition of the various proteins in a way and with a precision analogous to our analyses of simpler organic compounds. The introduction of the quantitative elementary analysis of organic compounds by Lavoisier around the year 1800 has inaugurated the splendid development of organic chemistry on the basis of the so-called structural theory. I hope not to be too much of an optimist in expecting that the recently developed methods for a precise constituent analysis of proteins may help to pave the way for an explanation of the biology of proteins on the basis of their molecular architecture. At this point, however, I should like to remind you that for an understanding of the architecture of a protein molecule it is not sufficient to know the nature and number of its amino acids. We must learn also by which linkages the amino acids are combined to one another and, furthermore, we must know the sequence of the amino acid residues within the protein molecule.

More than thirty years ago Emil Fischer (11), as well as Hofmeister (12), expressed the theory that the amino acid residues which constitute a protein molecule are combined one by one through CO—NH bonds, so-called peptide bonds, thus forming long chains containing many CO—NH groups. Three facts may be mentioned in support of this peptide theory:

- (1) By the hydrolysis of proteins, basic as well as acidic groups are formed, as would be expected if peptide linkages are broken.
- (2) After an incomplete hydrolysis of proteins, fragments that are known to contain peptide bonds can sometimes be isolated.



(3) Many synthetic peptides are split by enzymes that occur in the intestinal tract and in the tissues of human beings and of animals.

Through the irony of fate, the latter fact subsequently became the greatest obstacle to the peptide theory. When the Willstätter school of enzyme chemistry found a way to fractionate the proteolytic enzymes of the gastrointestinal tract and those of other sources, it became necessary to differentiate between the peptidases that attack the peptide linkages of low molecular peptides and the proteinases, such as pepsin and trypsin, that attack higher molecular proteins. None of these proteinases that digest high molecular proteins was found capable of digesting simple peptides—neither natural nor synthetic peptides. There was considerable discussion as to how to reconcile the peptide theory with the fact that proteins are digested by enzymes which do not attack the peptide bonds of all the known low molecular peptides. In order to reconcile the experimental facts with the peptide theory it has been assumed, and held until very recently, that proteinases are restricted to substrates of very high molecular weight. On the other hand, it has repeatedly been suggested that proteins may contain large numbers of linkages that differ from peptide bonds and may be the points at which pepsin, trypsin, and other proteinases attack the protein molecule. None of these hypotheses has found, or could be expected to find, sufficient experimental support as long as we had to restrict our experiments with proteinases to the digestion of genuine proteins. Let us assume, for instance, that we subject a protein containing, say, 576 amino acid residues to the digestive action of pepsin, and let us furthermore assume that the enzyme splits the protein into about 50 fragments. There is no experimental method at our disposal that would permit the separation from one another and the characterization of these 50 fragments. Consequently, it is not possible to establish the site of cleavage in the original protein molecule or to determine the exact nature of the many linkages that were split.

In recent years, however, with my associates, Doctors Fruton, Zervas, and Ross (13-19), we have succeeded in overcoming these experimental difficulties by the application of artificial low molecular protein models instead of genuine high molecular proteins. By means of the synthetic methods developed in our laboratory, a great number of such protein models were constructed. These simplified proteins contain only a few amino acids combined by peptide bonds—that is, in a definitely known arrangement. Despite their simple structure and their extremely low molecular weight, these protein models are digested by proteinases under exactly the same conditions as are genuine proteins. Upon digestion, our protein models yield only two or three fragments which can easily be isolated and characterized. Consequently, the site of the enzymatic action and the nature of the cleaved linkage can be established without great difficulty. For each of the known proteinases it was possible to

synthesize numerous simple substrates. A few of these artificial substrates are listed in table VI. These synthetic protein models may be used to advantage in a study of protein digestion. It was found, for example, that each proteinase has its individual specificity and therefore its individual substrates. However, in spite of this highly developed specificity, all of these enzymes have one property in common: namely, they are specifically adapted to the splitting of peptide bonds—that is, of CO—NH linkages. All our specific substrates, as for example those reported in table VI, contain several peptide bonds. However, every peptide bond in each of the substrates possesses a different specific value with respect to enzymatic digestion, dependent upon the nature of the amino acids that participate in the peptide bond. In the first synthetic substrate of Table VI the peptide bond between the glutamyl residue and the tyrosine residue is split by pepsin but not by trypsin or chymotrypsin. The peptide bond in benzoylarginineamide is hydrolyzed by trypsin but not by pepsin or

TABLE VI  
*Synthetic substrates for proteinases*

ENZYME	SUBSTRATES
Pepsin	Carbobenzoxy- <i>l</i> -glutamyl- $\dot{\vdash}$ - <i>l</i> -tyrosine
Trypsin	<div style="display: flex; align-items: center;"> <span style="font-size: 2em; margin-right: 5px;">{</span> <div style="margin-left: 5px;">           Benzoyl-<i>l</i>-arginine<math>\dot{\vdash}</math>amide            Benzoylglycyl-<i>l</i>-lysine<math>\dot{\vdash}</math>amide         </div> </div>
Chymotrypsin	Benzoyl- <i>l</i> -tyrosyl $\dot{\vdash}$ glycineamide
Papain	Benzoylglycineamide

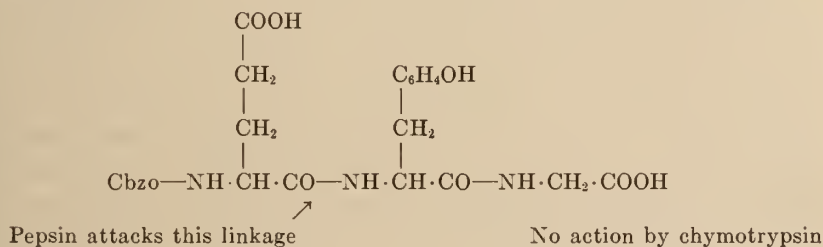
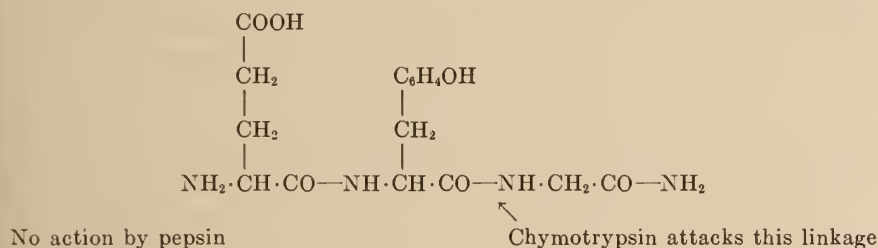
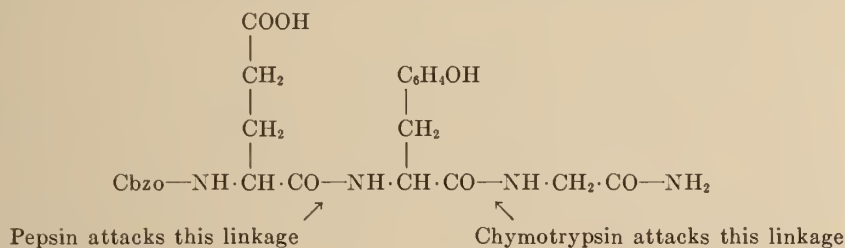
chymotrypsin. Thus it becomes quite evident that each of the proteolytic enzymes which are present in the gastrointestinal tract and in the tissues of human beings has a sharply defined specific task. I should like to illustrate this (table VII) for the enzymes pepsin and chymotrypsin, by comparing their action upon the same substrate. Both enzymes have been found to attack one of our synthetic protein models which has the rather lengthy name of carbobenzoxyglutamyltyrosylglycineamide. This substrate has several peptide bonds. Pepsin, as well as chymotrypsin, splits only a single peptide bond in the substrate, but pepsin splits a peptide bond other than that split by chymotrypsin. Pepsin action occurs at the peptide linkage between the glutamyl and tyrosyl residues, while chymotrypsin action takes place between the tyrosyl and glycyl residues. One is forced to conclude that different enzymes attack a protein molecule at different peptide linkages, and hence the course of the digestion of a protein must depend upon the specificity of the enzyme that performs the

first digestive attack. This is a consequence of quite some significance—namely, that a protein may yield fragments of rather different biological value, depending upon the specificity of the enzyme which produces the fragments from the protein.

In studying, by means of synthetic substrates, the factors which influence protein digestion, we may modify the electrochemical character of our

TABLE VII  
*Relative specificity of pepsin and chymotrypsin*

Carbobenzoxy-*l*-glutamyl-*l*-tyrosyl-glycine amide



substrate carbobenzoxyglutamyltyrosylglycineamide (table VII). For example, we may remove the carbobenzoxy group, thus uncovering the basic amino group. The resulting glutamyltyrosylglycineamide is no longer split by pepsin, because the presence of the basic amino group affects the specific value of the neighboring peptide bond, making it resistant to pepsin action. In contrast to pepsin, chymotrypsin is not

inhibited by the presence of the amino group and acts at the same peptide bond as before. If, on the other hand, we test the compound carboben-zoxyglutamyltyrosylglycine, in which the acidic carboxyl group is uncovered, pepsin hydrolyzes the compound, while chymotrypsin is no longer effective. The decisive influence of the basic and acidic groups upon the action of the proteinases was not known previously, and therefore all efforts for a closer study of the specificity of these enzymes had to remain fruitless.

As I have mentioned before, all the known enzymes which digest genuine proteins could be demonstrated to be specifically adapted to the splitting of peptide bonds. No other types of amino acid compounds were found to be attacked by these enzymes. There can be no doubt, therefore, that the digestive action of protein-digesting enzymes upon proteins must be concerned with peptide bonds. We no longer have to fear that proteins contain large numbers of linkages of unknown nature but can without reservation consider the peptide bonds to form the essential links connecting the amino acid residues inside a protein molecule. Since the beginning of this century it has frequently been suggested that each peptide linkage may be able to exist in two isomeric forms and that the various peptide bonds of a protein molecule may interact with one another. These suggestions have hitherto not led to clear-cut experimental results of any kind; however, they do not affect the essential points of our discussion.

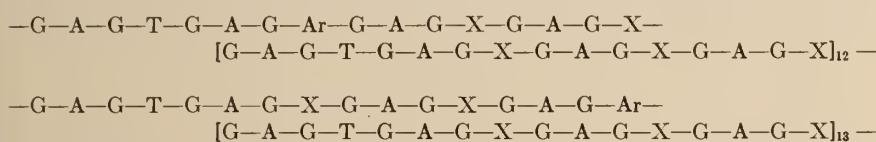
The peptide theory gives the general scheme by which the amino acids are linked to one another within a protein molecule. But there still remains the question as to the sequence of the various amino acid residues that constitute the molecule of an individual protein. In order to find an approach to the structural sequence of the amino acids in proteins, let us consider once again the numerical rules governing the composition of protein molecules (table V). The regularities are so striking that one is forced to assume that their basis lies in the sequence of the amino acid units that constitute the protein molecule. The distribution of these units may be such that it includes by implication the numerical rules found experimentally. The structural principle resulting from these conclusions (20, 21) may be illustrated by the example of silk fibroin. Table VIII describes a segment of the fibroin molecule in a way so that every second amino acid unit is a glycine residue; every fourth residue is an alanine residue; every sixteenth residue is a tyrosine residue; and every two hundred and sixteenth is an arginine residue. If this picture is correct, then as a general rule the amino acid residues of a protein molecule may be arranged in such a way that each individual residue repeats itself throughout the protein molecule at constant intervals—that is, with a regularly recurring frequency. In general, the frequencies are different with respect to the various kinds of amino acid residues of the same molecule. The protein molecule thus would contain a number of different,



superimposed frequencies. This principle of the superimposed frequencies confers a relatively simple, yet unique structural pattern upon the giant protein molecule. Within this general scheme various proteins may differ with respect to the chain length of their molecules and to the nature and the frequencies of their constituents. For example, the fibroin of the silk fiber holds a quite singular position in repeating the simplest neutral amino acid, glycine, with so low a frequency as 2 (table IX). There is another group of fibrous scleroproteins that contain glycine with a frequency of 3: namely, skin collagen, tendon collagen, and elastin. The low frequencies with which the neutral glycine residue repeats itself within these proteins offer an explanation for the biological function of these proteins as inert

TABLE VIII

*Structural pattern of silk fibroin (a segment of the molecule)*



The symbols *G*, *A*, *T*, and *Ar* refer respectively to the residues of glycine, alanine, tyrosine, and arginine. The symbol *X* represents an amino acid the nature of which will not be discussed here.

TABLE IX

*Frequencies of glycine in several proteins*

Silk fibroin		—G—X—G—X—G—X—G—X—G—X—G—X—
Skin collagen	} Cattle	—G—X—X—G—X—X—G—X—X—G—X—X—
Achilles tendon		
Elastin		

fiber materials and for the crystalline character of the fibers as revealed by their respective X-ray diagrams.

In the course of this lecture I have repeatedly mentioned that living organisms do not produce the infinite number of proteins that would be possible if the nature, number, and sequence of amino acids could be varied unrestrictedly. Only those proteins that exhibit simple numerical rules and the pattern of the superimposed frequencies seem to occur in nature. One wonders what may be the reason for this limitation. It appears that the limitation in the number and types of naturally occurring proteins must have its basis in the mechanism of the biological formation of proteins. In collaboration with Doctors Conrat, Behrens and Fruton, we have approached the problem of the physiological formation of proteins experimentally in the belief that the formation of proteins must be an

enzymatic process and that the same enzymes that hydrolyze proteins must also be responsible for their biological synthesis (22, 23, 24). In order to obtain clear-cut results the method of specific models was again used. In this way it could be shown that proteinases such as chymotrypsin, cathepsin, and papain are by no means restricted to hydrolytic reactions but catalyze also syntheses. The enzymatic synthesis of peptide bonds may be described by a few examples (table X).

The first example describes the combination of benzoylleucine with leucine anilide to form benzoylleucylleucine anilide under the influence of the enzyme papain. This reaction involves the synthesis of a true peptide linkage between two leucine residues. Example 2 reports the enzymatic synthesis of a peptide bond between phenylalanine and leucine. Examples 3 and 4 describe the enzymatic combination of 3 or even 4 amino acid residues through genuine peptide bonds. Reactions 5-6 represent syntheses of peptide bonds produced by the pancreatic enzyme chymotrypsin.

TABLE X  
*Synthesis by proteolytic enzymes*

---

<i>Enzyme: Papain</i>	
1. Benzoyl leucine + leucine anilide	→ Benzoyl leucyl leucine anilide
2. Benzoyl phenylalanine + leucine anilide	→ Benzoyl phenylalanyl leucine anilide
3. Carbobenzoxy phenylalanyl glycine + tyrosine amide	→ Carbobenzoxy phenylalanyl glycyl tyrosine amide
4. Acetyl phenylalanyl glycine + glycyl leucine	→ Acetyl phenylalanyl glycyl glycyl leucine
<i>Enzyme: Chymotrypsin</i>	
5. Benzoyl tyrosine + leucine anilide	→ Benzoyl tyrosyl leucine anilide
6. Benzoyl tyrosine + glycine anilide	→ Benzoyl tyrosyl glycine anilide

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These and many other synthetic reactions are performed by the same proteolytic enzymes which also perform the well-known hydrolytic processes of protein digestion. Whether, under given circumstances, these enzymes perform a synthesis or a degradation is determined by specificity phenomena and by the thermodynamic conditions.

Let us consider first, and rather briefly, the influence of specificity phenomena. That various enzymes act differently has already been mentioned and needs no further illustration. At this point of our discussion we are more interested in the fact that a single enzyme may act differently on various substrates and that rather small changes of the substrate structure may shift the place of enzymatic action or alter the type of reaction. In table XI we compare first the action of papain upon three substrates of identical chain length and identical general type. All three are composed only of the aliphatic amino acids glycine and leucine. However, despite this similarity, substrate 1 is hydrolyzed at

another place, relative to the two molecule ends, than is substrate 2; and substrate system 3 undergoes a synthetic reaction, not a hydrolysis.

The next group of two rather similar substrates shows an enzymatic hydrolysis in one case and, when a tyrosine residue is added, an enzymatic synthesis.

The last group of substrates deals with the action of the enzyme chymotrypsin. Whether a peptide linkage between a tyrosine and a glycine residue is split or produced is decided upon by the difference between groups remote from the place of enzymatic action. The various reactions reported in tables X and XI demonstrate that the specificity of proteinases is exactly of a kind such as might be expected from enzymes capable of synthesizing the unique patterns of individual proteins. The specificity of proteinases is characterized by the experimental finding that a proteinase

TABLE XI  
*Interdependence of substrate structure and enzymatic action*

	Benzoyl leucyl glycyl   glycine	Hydrolysis
(Papain)	Benzoyl leucyl   leucyl glycine	Hydrolysis
	Benzoyl leucine+leucine anilide	Synthesis
	Benzoyl phenylalanyl glycine   amide	Hydrolysis
(Papain)	Acetyl phenylalanyl glycine+tyrosine amide	Synthesis
	Benzoyl tyrosyl   glycine amide	Hydrolysis
(Chymo- trypsin)	Benzoyl tyrosine+glycine anilide	Synthesis

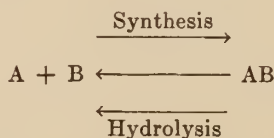
is capable of producing a variety of reactions and of reacting on a variety of peptide bonds. Nevertheless, in general the enzyme performs only one unequivocal reaction at each individual peptide bond.

During the synthesis of a protein molecule, several hundreds or thousands of peptide bonds are formed. In each single step of the synthesis the synthesizing enzyme has to act on a different substrate and by its action in one step it removes the reaction products of the foregoing step and synthesizes the substrates of the next step.

In mentioning the fact that the biological synthesis of a protein consists of a long sequence of single reaction steps, wherein one step removes the reaction products of the foregoing step, we approach the thermodynamic angle of the biological synthesis of proteins. Considering the thermodynamic angle, the question may be raised: Which are the driving forces in protein hydrolysis and protein synthesis? In order to find an answer

to this question, let us discuss the case that an enzyme acts upon a protein AB and its split-products A and B. Then, the hydrolysis of AB into A + B is in competition with the synthetic process which combines A and B into AB.

*Scheme of an equilibrium reaction*



The hydrolysis and the synthesis of a peptide linkage are in equilibrium with each other, the enzyme being the catalyst which accelerates the establishment of the equilibrium.

The equilibrium between the hydrolysis and the synthesis of a peptide linkage which is established by a proteolytic enzyme is always predominantly on the side of the hydrolysis since, in general, the products of the hydrolysis are on a lower level of energy. In homogeneous solution, the thermodynamic tendency for the synthesis of a peptide bond is very small. Nevertheless, these unfavorable thermodynamic conditions are overcome in the biological synthesis of proteins. It is a well-known fact that it is possible to force an equilibrium reaction to proceed uphill, towards the higher energy level—in our case, that is towards the synthesis of peptide bonds. It is necessary only to keep the concentration of the synthetic product continuously at a value below the equilibrium concentration. In order to effect this, the biological synthesis of proteins follows two principal methods. One method is to perform the protein synthesis in an inhomogeneous solution. As soon as small amounts of protein are synthesized, they are deposited or carried away by the circulatory system. The second method of synthesis is applied in a homogeneous solution. In this case a multitude of synthetic steps follow one another and in this reaction sequence the synthetic product of the first step is at once used up by the second, the products of the second step by the third, and so forth.

In order to prove the validity of these thermodynamic considerations, it was necessary to perform both types of enzymatic peptide syntheses *in vitro*. The first type, the synthesis in an inhomogeneous system, is realized in most of the previously mentioned model experiments in which peptide linkages were synthesized by enzyme action. When we perform the enzymatic synthesis of one of our protein models, the synthesized protein model crystallizes out and is thus continuously removed from the equilibrium. In order to restore the balance of the equilibrium reaction, the synthesis proceeds, more synthetic product crystallizes, and so forth. The second type, the synthesis of a peptide bond in a homogeneous solution, may be illustrated in table XII. This table deals with a recently



discovered type of enzymatic reaction which consists of three single steps (25). In the present discussion our interest is concentrated principally on the first step. Two peptides, acetyl phenylalanylglycine and glycyl-leucine, are treated with the enzyme papain in aqueous solution. To a very small extent, they combine by an equilibrium reaction to form acetyl phenylalanylglycylglycylleucine. In the same solution and under the influence of the same enzyme, this small amount of synthetic product undergoes a second and a third reaction step and is thus removed from the first equilibrium reaction. In consequence, the first equilibrium continues in the direction of the synthesis and finally all of the glycylleucine is used up by a synthetic reaction. The second and third steps of this reaction sequence provide the driving forces for a completion of the first step which consists in a synthesis.

Experimental syntheses like those demonstrated in several of the tables show that proteolytic enzymes possess the qualities of enzymes performing protein syntheses; and the same experiments also give us information about

TABLE XII

*Synthesis in homogeneous solution*

---

Acetyl phenylalanyl glycine + Glycyl leucine
↓↑↑
Acetyl phenylalanyl glycyl glycyl leucine
↓↓↑
Acetyl phenylalanyl glycyl glycine + Leucine
↓↑↑
Acetyl phenylalanyl glycine + Glycine

---

the general conditions under which the enzymatic protein synthesis proceeds. Until very recently, it was assumed that proteolytic enzymes under normal physiological conditions are restricted to protein degradation and that special conditions of concentration, pH, and oxygen pressure are necessary for protein synthesis—especially for the syntheses connected with certain pathological growth processes. The recent model experiments, however, have provided ample evidence for the fact that protein hydrolysis and protein synthesis proceed under identical general conditions. Therefore, whenever and wherever a proteolytic enzyme in our tissues comes into contact with a protein and protein constituents, the conditions are given for a competition between hydrolytic and synthetic reactions. Peptide linkages are synthesized and hydrolyzed simultaneously and uninterruptedly in our cells, under the catalytic influence of proteinases. The highly developed specificity of these enzymes forces the processes of synthesis and degradation to run along predetermined lines, thus resulting in the specific proteins which are characteristic and indispensable for each individual organism. Consequently, in a certain sense we are

the products of the specificity of our proteinases; and therefore we hope in the future to extract much valuable information about ourselves from a closer study of the specificity and the specific action of our proteinases.

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## A CASE OF ILEITIS WITH AN UNUSUALLY PROLONGED COURSE

JOHN H. GARLOCK, M.D.

[From the First Surgical Service]

The following case is of particular interest, since it was one of the first instances of terminal ileitis seen at The Mount Sinai Hospital.

### CASE REPORT

*History* (Adm. 404384). S. R., a young woman of 24 years, was first admitted to The Mount Sinai Hospital in July 1927. She complained at that time of intermittent pain in the right lower quadrant of four months' duration, with anorexia and a loss of fourteen pounds. For four days preceding admission she had noted fever. The past history was important in that an appendectomy was performed eight years before for a ruptured appendix with abscess. Two years later another operation was performed for "adhesions."

*Examination.* The patient appeared acutely ill; temperature was 103.4°F. There was marked tenderness in the right lower quadrant where a mass could be felt.

*Operation.* The patient was operated upon and there was found an abscess in the right lower quadrant with thickening of the terminal ileum, cecum, and ascending colon. The operative note reads, "Appendix not found. Five to six inches of the terminal ileum were greatly distorted, with thickening of the wall and an opaque color. No collection of pus was found in the bowel wall. In freeing the ileum in the region of the ileocecal junction the gut was entered bluntly. This opening was closed by interrupted stitches."

*Course.* Postoperatively, the wound drained profusely and a fecal fistula developed. A few weeks later an anastomosis was made between the terminal ileum and the transverse colon with exclusion of the ileum. The fecal fistula closed spontaneously and the bowels moved normally thereafter. The patient was discharged four months later.

*Second Admission* (December 1927). The patient's complaint was discharge of mucoid material from the sinus in each incision. A roentgenogram after injection of lipiodol apparently failed to show any communication with the bowel.

*Third Admission* (November 1928). Her complaint at this time was a discharging sinus in the right lower quadrant with occasional bouts of fever. An operation was performed on December 7, 1928. At this time both sinuses were found to communicate with each other and to enter an abscess cavity in the right lower quadrant. The cavity was packed with gauze. The patient was discharged from the hospital two months later.

*Interval History.* During the following six years the patient was admitted on five occasions for abscesses in the abdominal wall in the region of the sinus which never healed. Actinomycosis was looked for repeatedly, but never demonstrated. Cultures were inconclusive. Repeated X-ray examinations of the gastro-intestinal tract were reported negative.

*Fourth and Final Admission* (February 8, 1937). At this time lipiodol was again

injected into the sinus tract. Upon X-ray examination, the lipiodol was seen to enter a cavity, rounded in outline, which extended downwards along the right wall of the pelvis and apparently did not communicate with the bowel. A diagnosis of terminal ileitis was suggested and the patient was operated upon on February 23, 1937.



FIG. 1. Photograph of gross specimen showing the terminal ileum, ileocecal junction and cecum. A double stricture may be noted: (1) at the ileocecal region, and (2) in the terminal ileum about two inches proximal. The sinus opening is indicated by the arrow.

*Operation.* (Avertin, gas-oxygen, ether anesthesia). An incision was made near the midline. There was considerable difficulty in entering the peritoneal cavity because of the presence of extensive adhesions. These included the great omentum and loops of small bowel adherent to the anterior abdominal wall. Sharp dissection was necessary to free the various loops of intestine. The anastomosis between the ileum and transverse colon was demonstrated and appeared to be free of inflammatory infiltration. Extending from this region was a loop of small bowel which was curled upon itself, densely adherent to the ileum proximal to the ileo-colostomy, and which terminated in a dilated loop of ileum situated along the right wall of the pelvis. Behind and above this loop was an indurated mass composed of ileum, cecum, and infiltrated mesentery. Into this mass passed the sinus tract. The entire mass was separated from the posterior abdominal wall and delivered into the wound. There presented now an unusual picture of markedly thickened terminal ileum with a stricture just beyond the dilated loop and another at the ileocecal junction. The sinus was seen to extend directly into the cecum and terminal ileum. The entire mass was removed after division of the ascending colon. The remaining stump of colon was triply inverted. Two cigarette drains were placed through the original sinus wound and the operative incision was closed without drainage. An ovarian cyst, the size of a small grapefruit, was seen in the left side of the pelvis, but this was not disturbed. The patient's convalescence following this procedure was uninterrupted and she was discharged on March 13, 1937, with both wounds solidly healed.

*Pathological Report:* The specimen, (fig. 1), consists of a resected portion of ileum, cecum and ascending colon along with the corresponding portion of mesentery. It has been opened longitudinally. The specimen is distorted by a marked infiltration and thickening of the mesentery of the terminal ileum and at the ileo-cecal junction. In

addition, there are numerous adhesions which cover the entire resected specimen. The ileum measures approximately 27 cm. in length. Its serosal surface is congested and covered by adhesions. The wall is thickened throughout, but es-



pecially in its more distal portion. The mucosa is edematous, thickened and injected. Many of the rugae are obliterated. The thickening and infiltration of the ileum increases as the ileo-cecal junction is approached. Two strictures are present. In the mid-portion of the ileum approximately 10 cm. from the ileo-cecal junction, there is a definite constriction. In this region, a shallow ulceration is to be seen. This is irregular in outline and approximately 0.5 cm. in diameter. Another stricture is to be noted 4 cm. proximal to the ileo-cecal junction. At this point a sinus opening 0.5 cm. in diameter is present on the mesenteric surface of the ileum. An irregular sinus tract can be probed in several directions. The probe can be passed: 1) directly into the cecum through an opening situated 1.75 cm. beyond the ileo-cecal valve; 2) through the ileum in the region of the mesentery at the ileo-cecal junction, and 3) blindly into the firmly infiltrated tissue at the ileo-cecal junction. The cecum and ascending colon measure 13 cm. in length. The serosal surface here is likewise covered with adhesions. The mucosa appears somewhat edematous. About the cecum and in the mesentery of the ileum, there is a marked inflammatory infiltration including several large nodes. Microscopic examination revealed chronic ulcerative ileitis.

*Follow-up.* The patient has remained well except for symptoms referable to the ovarian cyst. Recently a dilatation and curettage was performed on the Gynecological Service and the irregular bleeding which was the main complaint has disappeared. The bowels move normally and there is no abdominal pain. The patient has gained thirty pounds.

#### COMMENT

Twelve years ago terminal ileitis was not the well-defined disease entity which it is today and, as is obvious from the operative and other notes, there was considerable doubt as to the exact nature of the disease. In the light of our present knowledge, however, there would be little difficulty in diagnosis today.

The repeated lipiodol injections did not appear to enter the small bowel, but re-examination of the X-ray plates today, alongside the pathological specimen, shows that the lipiodol entered the dilated loop of terminal ileum but was prevented from going further by the stricture at the ileo-cecal junction.

This patient is an exception to the usual experience that abdominal wall sinuses complicating regional ileitis usually close spontaneously after a short-circuiting operation with exclusion of the diseased bowel.

Whether these patients will remain well after a short-circuiting operation alone is a question that cannot be definitely answered as yet. There is no doubt that many of these patients improve markedly and seem free of symptoms, but the postoperative follow-up period is too short at the present time to permit of definite prognostic statements on this score. Experiences in recent months with a few cases requiring secondary resection of the diseased bowel after a one- or two-year period of freedom from symptoms, lead one to feel that the final story of this curious disease has not as yet been told.

## DIVERTICULUM OF THE FEMALE URETHRA<sup>1</sup>

### REPORT OF A CASE

A. HYMAN, M.D., AND H. E. LEITER, M.D.

[From the Surgical Service of Dr. A. Hyman]

The earliest reference to diverticulum of the female urethra is that of a case treated by Hey (1) in 1786. It was not until many years later that Foucher (2), Priestley (3), and Tate (4, 5) reported the next few cases, and by 1894, Cullen (6) was able to collect thirty-seven cases from the literature. Since then, many papers have appeared and the more recent authors have been able to present a number of instances which have come under their own observation. Although this condition is uncommon, its recognition is important, since the removal of these diverticula results in a spectacular relief of the patient's symptoms.

Diverticula of the urethra in women are either acquired or congenital in origin. The acquired forms result from trauma which causes a break in the urethral mucosa, or from the infection of a urethral gland or lacuna. Dawson Furniss (7) believes that most of these diverticula are secondary to suburethral abscesses which result from closed off infected urethral glands or lacunae and subsequent recommunication of the abscess with the urethra. He describes numerous glands and lacunae on the floor of the urethra on either side of the median *crista urethrae*. In contrast to this statement is the recent report of Cabot (8) which offers proof that glands are normally absent in the posterior two-thirds of the female urethra. Nevertheless, most of the diverticular openings are in the middle third of the urethra, on either side of the midline.

The congenital variety is secondary to (1) a Gartner's duct, (2) a Wolffian duct, (3) cell rests, (4) vaginal cysts, and (5) faulty union of the primary folds in the midline (Johnson (9)). That this form exists is evidenced by the reports of diverticula in the newborn and in a child one year of age.

The wall of the diverticulum is composed mainly of fibrous tissue through which inflammatory cells are dispersed. An epithelial lining may or may not be present. It is usually absent where the contents have been frankly purulent. When present, it may be composed of squamous, columnar, or cuboidal cells. At times calculi have been present in these diverticula (Shivers and Cooney (10), Hunner (11)). These calculi are

<sup>1</sup> Read before the Section of Genito-Urinary Surgery at the New York Academy of Medicine, March 15, 1939.

either due to stones from above which were caught in the urethral pouch or result from the deposition of salts around a foreign body as a nucleus. A patient can have more than one diverticulum in the urethra. Furniss had four patients with paired diverticula.

The smaller pouches may be asymptomatic. The larger ones can give rise to urethral or perineal pain, dyspareunia, pain on sitting, vaginal mass, discharge of pus from the vulva, recurring cystitis, persistent urinary infection, and other urethral and bladder symptoms. The dysuria and pain may be worse during micturition, at which time the increased intra-urethral pressure distends the diverticulum. Following urination, a small amount of leakage can occur when the patient assumes the standing position; this is due to the slow emptying of the previously filled pouch.

In Hey's case there are to be noted the following findings: a mass in the floor of the urethra, pressure upon which caused pus to exude from the meatus; a clear urine on catheterization of the bladder; and, finally, free passage of a bent probe through the external urethral meatus into the pouch. Most authors stress the importance of a sub-urethral mass which is to be differentiated from a cystocele of the bladder. Our patient failed to show this sign. The diagnosis is usually confirmed by urethral endoscopy combined with urethrography and contrast cystography.

The smaller pouches can be treated conservatively. Some of the patients learn to empty the sac themselves by placing a finger in the vagina. The larger pouches require surgical excision through the vagina, closure of the urethral opening of the diverticulum, and the use of an indwelling urethral catheter for a period of one to two weeks. Urinary incontinence following operation is uncommon unless the urethral sphincter is injured. The patient is usually promptly relieved of her distressing symptoms.

#### CASE REPORT

*History* (Adm. 440695). E. L., a white married woman, 42 years of age, was first seen at our office on May 15, 1937. For more than ten years she had had frequency and pain during micturition. She voided every hour during the day and three to four times at night. Most of her pain occurred during urination and would shoot into the left side of her vulva and into the upper inner aspect of her left thigh.

On examination, the urethra appeared slightly thickened and was sensitive to pressure. Passage of a catheter along the urethra was very painful. Cystoscopy under spinal anesthesia showed a diffusely inflamed bladder.

The catheterized bladder and kidney urines were sterile on culture and showed no pus on microscopic examination. Flat X-ray examination of the abdomen and excretory urograms were normal.

The patient then left the city and, while away, was cystoscoped a number of times by several urologists. On one occasion the posterior urethra was fulgurated. Following this procedure her local symptoms became aggravated. She returned to our care January 11, 1938 and was admitted to The Mount Sinai Hospital.

*Examination.* Cystoscopy under spinal anesthesia showed a normal bladder. There was no evidence of elusive ulcer of the bladder. Urethroscopy with the McCarthy panendoscope was then done. On the floor of the urethra to the left of

the midline and at the region of the middle and distal third of the urethra, there was a circular opening. A #5 ureter catheter was passed into this opening for a distance of 30 centimeters. X-ray pictures were then taken, including a contrast cystogram (fig. 1). A vaginal examination by one of the gynecologists revealed no abnormality and no sub-urethral swelling.

*Operation* (by Dr. Hyman under avertin anesthesia). A ureter catheter was first passed into the diverticulum through a cystoscope as a guide to the diverticulum. A large catheter was also placed in the urethra. A midline incision was then made in the urethro-vaginal septum. The diverticulum was about one and three-quarters inch in length, extended proximally, and was adherent to the bladder and urethra. It was dissected away from the bladder and urethra. The opening in the urethra was closed by ligating the neck of the sac. Interrupted sutures were then placed in the periurethral tissues on either side to make a buttress over the floor of the urethra. The mucosa was then closed and the urethral catheter was left indwelling.

After the removal of the indwelling catheter twelve days later, the patient voided for the first time without pain. The bladder was filled with 250 cubic centimeters



FIG. 1. Roentgenogram showing bladder filled with 5 per cent sodium iodide and the coiled up ureteral catheter in the diverticulum of the urethra.

of blue colored solution and a vaginal tampon inserted. After voiding, the tampon was not stained blue, demonstrating the absence of leakage.

At the present time, the patient feels perfectly well and has no urinary frequency or pain.

#### SUMMARY

Diverticulum of the female urethra can be easily overlooked. It gives rise to numerous lower genito-urinary tract symptoms. If the condition is borne in mind, it can be readily diagnosed by urethroscopy and urethrography. The smaller diverticula can be treated conservatively. Surgical excision of the larger diverticula results in a spectacular relief of the patient's symptoms.

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## LOCALIZED ACUTE PHLEGMONOUS COLITIS

### CASE REPORT

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[From the Surgical Service of Dr. J. H. Garlock]

Localized acute ulcerative non-specific colitis, comparable to the lesion found in the case to be described, is usually designated in the literature as acute phlegmonous colitis. Most of the instances have been recorded in the Scandinavian literature, Bohmansson (1) having collected a total of thirty cases. Several more cases have been reported by Braun (2), Elving (3), Crane (4), and Bunch (5). The descriptions of the pathology are fairly uniform. Crane states, "A definite thickening of the bowel wall obtains which forms a distinct tumor involving most of the coats. The starting point of the inflammatory reaction is almost invariably in the muscularis layer of the bowel, or in the submucosa. Sections show a diffuse fibro-blastic proliferation with lymphoid and plasma cell infiltration. There is usually a distinct polymorphonuclear infiltration occurring near the peritoneal coat. The mucosa itself is apparently spared until late in the process and then the change is usually evidenced as pressure atrophy." Rankin (6) also states that the lesion is confined mostly to submucosa at first but adds that destruction of mucosa from ulceration and necrosis is common. In Elving's case, the epithelium of the glandular crypts was missing in places and the crypts were full of bacteria (streptococci and colon bacilli). In our case, as will be seen, the earliest changes were very definitely in the mucosa, the other coats being secondarily involved. Of interest is the relatively subacute course with at least ten days of known septic temperature before abdominal tenderness was noted. (It is interesting also to speculate as to the preexistence of a similar low-grade process of long duration.) The etiology of comparable lesions has been thought to be of traumatic origin. The Scandinavians mention scratching of the mucosa by fish bones or other foreign bodies. Trauma caused by hard fecal masses has also been described. The presence of a more chronic lesion, as well as the acute process, is suggested by the pathological findings.

### CASE REPORT

*History.* (Adm. 430232). The patient, a white male of 56 years, was admitted to the medical service of The Mount Sinai Hospital on September 29, 1938. He was born in Germany and had lived in the United States for thirty years. He was an estimator by occupation. He had had scarlet fever at the age of 4 and gonorrhea at

the age of 22. About one and a half years prior to his admission to the hospital, he passed a fairly large amount of dark red blood by rectum, which he attributed to the presence of hemorrhoids. There was no recurrence. During the eight months before admission he lost 63 pounds. This was accompanied by the gradual development of severe anorexia and increasing weakness. About two months before admission he noted the appearance of marked pallor. This was in marked contrast to his usual florid complexion. Four weeks before admission he began to pass greenish-gray, loose, foul stools, twice daily. He also had epigastric burning after eating, relieved by alkalies, which did not improve on a Sippy diet. Two weeks before admission he had a mild shaking chill lasting five minutes and from then until admission ran a low-grade fever. Slight chronic constipation, which had been present for many years, had not increased during the period of illness. The patient had been receiving sulfanilamide (Gr. XXX q.i.d.) for one week before admission.

*Examination.* The patient was a well-developed male with a hectic flush involving the malar eminences, showing severe weight loss. The conjunctivae were suffused. The pharynx and tonsils were chronically inflamed. The chest was emphysematous. Dilated venules were noted over the lower thorax. Both chests moved equally but with diminished excursion. Breath sounds were generally diminished. Numerous fine crepitant râles were heard at the right base posteriorly, which persisted after coughing. The heart was enlarged to right and left. The right border of dullness extended to the base of heart, giving the impression of an enlarged left auricle. Sounds were of fair quality;  $P_2$  was lower than  $A_2$ . The rhythm was regular and rapid. Inconstantly, over the precordium an irregular friction rub was heard, consisting of clicking and scraping sounds. This rub was most audible at the end of expiration. There was moderate sclerosis of the radial vessels. Blood pressure was 115 systolic and 75 diastolic. Temperature on admission was 101.8°F.; pulse, 92 per minute; respirations, 22 per minute.

The abdomen was soft and not distended. There was no tenderness or rigidity. On rectal examination several cord-like structures were felt. These were thought to be thrombosed internal hemorrhoids. There was no tenderness. No masses were felt. There was moderate grayish cyanosis of the finger nails, attributed to the sulfanilamide which the patient had been receiving. The impression on admission was that the patient was suffering from a gastric carcinoma with a complicating pneumonitis, and rheumatic heart disease with pericarditis.

*Laboratory Data.* Blood: hemoglobin, 60 per cent; red blood cells, 3,300,000; white blood cells, 13,300 (polymorphonuclear neutrophils: segmented, 41 per cent; non-segmented, 36 per cent; monocytes, 7 per cent; eosinophiles, 1 per cent; lymphocytes, 15 per cent). Sedimentation time, greater than two hours; Wassermann reaction, negative; urea nitrogen, 13 mg. per cent; sugar, 100 mg. per cent; cholesterol, 220 mg. per cent; cholesterol ester, 65 mg. per cent; icterus index (acetone method), 7; sulfanilamide, a trace. *Circulation studies:* Saccharine time, 12 seconds. The venous pressure was 4 cm. in the right antecubital vein and rose to 6 cm. when pressure was exerted in the right upper quadrant. *Urine:* appearance, cloudy; reaction, acid; specific gravity, 1.022; albumin, a very faint trace; sugar, negative. Microscopic examination showed an occasional hyaline cast and a rare white blood cell. *Stool:* appearance, greenish liquid; guaiac, 3 plus; Mantoux, 1:100,000, negative. Stool culture, B. Coli and Enterococcus; no ova or parasites found.

*Course*—The patient ran an increasingly septic temperature with afternoon rises from 103° on admission to 105.8°F. two days before operation (ten days after admission). Two blood cultures were negative. Proctoscopy shortly after admission revealed the rectal ampulla to be full of green liquid pus. The anal canal was not clearly visualized but showed diffuse inflammation and a fissure on the right lateral surface. On the fifth day in the hospital, the sedimentation time was 23 minutes.

Sigmoidoscopy a week after admission revealed one large deep anal fissure which undermined and ulcerated the anal mucosa. The edges were heaped up and indurated. Biopsies were negative. At the rectosigmoidal angle there was one polyp which appeared benign. A biopsy was negative. There was no evidence of neoplasm. X-ray examination of the large bowel with the barium enema showed a slight persistent irregularity in the outline of the lower descendens and sigmoid colon. There was moderate spasm suggesting an inflammatory process. No other abnormalities were noted. Gastro-intestinal X-ray examinations were unsatisfactory. X-ray examination of the chest showed no abnormality in the lungs; the left leaf of the diaphragm was somewhat elevated by a distended splenic flexure. An electrocardiogram showed QRS slurred and of moderately low voltage. R-T transition was depressed in leads I and II;  $T_1$  and  $T_2$ , diphasic;  $T_3$ , semi-inverted. The diagnosis was myocardial involvement. Repeated white blood cell counts showed a persistent leucopenia. [On October 4, the white blood count was 9,200 (polymorphonuclear neutrophils: segmented, 49 per cent; non-segmented, 20 per cent; lymphocytes, 22 per cent; monocytes, 8 per cent; eosinophiles, 1 per cent). On October 11, the white blood count was 6,400 (polymorphonuclear neutrophils: segmented, 40 per cent; non-segmented, 39 per cent; lymphocytes, 18 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent).] As the hemoglobin dropped to 49 per cent he was given on October 8 a citrate transfusion of 500 cc. Signs of a mild bilateral bronchopneumonia persisted.

Twelve days after admission (October 11) for the first time tenderness was noted on deep pressure in the left lower quadrant and adjacent flank. It was felt that the diagnosis rested between diverticulitis of the sigmoid with perisigmoidal supuration or phlebitis, or perforating carcinoma of the sigmoid with abscess and phlebitis of the veins of the mesentery. In spite of the patient's poor condition, operation was decided upon.

*Operation* (by Dr. John H. Garlock under spinal anesthesia—Jones solution (nupercaine) 9 cc.—lower left rectus incision). On opening the peritoneal cavity there presented a most unusual pathological picture: the sigmoid colon was dilated to twice its normal size. The wall of the bowel appeared alternately pink, grayish, bluish, and red. The bowel wall was markedly thickened. The tissues felt extremely warm to the touch. The process was sharply demarcated below, just above the recto-sigmoid, and above, at the lower limit of the descending colon. The mesentery was somewhat thickened and there were a few enlarged succulent lymph nodes. The remainder of the colon was visualized and found to be normal. The liver was normal. The patient was running a septic temperature pointing either towards abscess formation in the bowel wall or phlebitis of the veins of the mesentery. Simple diversion of the fecal stream proximal to the lesion would not have relieved the patient of his septic manifestations. Therefore, it was decided, in spite of the relatively poor condition of the patient, that an attempt should be made to remove this segment of the bowel with a wide section of its contiguous mesentery. An obstructive resection was carried out without much difficulty after freeing part of the descending colon. Separate clamps were placed on each limb of the colon and the involved segment removed between crushing clamps. The two limbs of the colostomy were brought together and sutured with a few stitches of chromic catgut. The remainder of the wound was closed loosely in layers. The proximal limb was under slight tension.

*Pathological Examination.* The specimen consisted of a resected segment of colon measuring 24 cm. The entire mucosa showed a uniform picture which was very striking. There were numerous linear transverse ulcerations, varying in length from 1 cm. to 5-6 cm. These ulcerations were extremely deep and penetrated practically to the serosa of the bowel. The bases of these ulcers were covered with nec-



rotic hemorrhagic debris and a grayish exudate. Due to these linear ulcerations, the bowel had the appearance of latticework, long rectangular islets of mucosa separated by deep ulcerations. In one small area, approximately 7 cm. in length, the mucosa showed marked atrophy. The islets of tissue between the ulcerations were covered with angry red hypertrophic mucosa. There were several small hyperplastic lymph nodes in the pericolic fat which were removed for study.

The microscopic preparations showed various stages of the process. A small one mm. superficial ulceration—apparently one of the most recent lesions—showed complete disruption of the mucosal glands with haphazard scattering of clumps of epithelial cells among the plasma cells, lymphocytes and polymorphonuclear leukocytes. These inflammatory cells had extended for a short distance into the underlying submucosa. Except for the intense engorgement of the vessels, the remainder of the wall in this region was not remarkable. Elsewhere, the more advanced stages were manifested by marked thickening of the mucosa, most of which had undergone almost complete necrosis, although remnants of a previous organization and cellular infiltration were apparent. Small areas of hemorrhage from ulceration of nearby vessels were abundant. Here and there, in the midst of this necrotic tissue, were areas of truly polypoid, quite intact mucosa. In some places, the thickened submucosa lay bare or was covered by a thin mantle of exudate. The entire wall, including the serosa, showed for the most part evidence of an acute inflammation, in the form of scattered nests of polymorphonuclear neutrophils, disrupting muscle and collagenous bundles, superimposed on an older organized process. There was no evidence of a primary vascular involvement. The diagnosis was acute extensive ulcerative colitis (non-specific). No evidence of phlebitis was found.

The postoperative course was singularly smooth. The temperature, which before operation had spiked daily to 105°F., reached a high of 101.8°F. on the third postoperative day, following which it fell gradually to normal. The colostomy, which was opened on the fourth postoperative day, functioned well. He was allowed out of bed on the fourteenth day. During the following ten days he gained fourteen pounds.

He was seen in the Follow-Up Clinic two months after discharge, at which time the following note was made: "General condition excellent. Has gained over thirty pounds. Colostomy was closed down considerably but should be repaired surgically."

The patient was recently readmitted to the hospital for closure of the colostomy. He had gained fifty pounds.

#### COMMENT

A logical explanation would suggest that a foreign body trauma caused the rectal bleeding noted one and a half years before admission and initiated a low-grade inflammatory lesion which caused the anorexia, weight loss, etc. during the eight months before the acute process supervened.

The excellent response of the patient to the operation of obstructive resection was gratifying. There have been four other cases of cure reported following obstructive resection—one by Dowd (7) of the descending colon, one by Van Saar (8) of the ascending colon, Elving's case in the sigmoid by electrocauterization, and one by Crane in the sigmoid. Elving's case recovered despite evidences of early peritonitis at operation.

Most of the reported cases had diffuse peritonitis at the time of operation due, in some instances, to demonstrable perforation. One case, reported

by Bunch, presented a massive intraperitoneal hemorrhage due to erosion of a large vein in the bowel wall by a perforating ulceration.

No cases have been reported in which the diagnosis was made pre-operatively. In this case, the possibility of an inflammatory lesion was seriously considered, but it was thought to be secondary to a diverticulitis.

The rapid progression of the disease and the high mortality in cases which have gone on to perforation and peritonitis leads to the conclusion that when acute phlegmonous colitis is found at operation the procedure of choice, whenever feasible, is resection of the diseased bowel.

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TOXIC HEPATITIS ASCRIBED TO THE USE OF CINCHOPHEN  
ILLUSTRATION OF THE ANALGESIC EFFECT OF JAUNDICE IN LONG-STANDING  
RHEUMATOID ARTHRITIS

S. S. LICHTMAN, M.D.

[From the Medical Service of Dr. George Baehr]

The following case merits interest because it raises the question of the relationship of the clinical effect of cinchophen, used to relieve joint pains, to the development of jaundice and the subsequent beneficial effect of the jaundice upon these joint pains.

CASE REPORT

*History* (Adm. 432288). A wood carver, aged 47 years, noticed progressive loss of strength over a period of three weeks. He found it difficult to complete his day's work. Simultaneously, he noted a complete loss of appetite and an increase in habitual constipation. He moved his bowels only once, in five days. For a day he suffered pain in the right lower quadrant of the abdomen, which radiated to the small of his back and between his shoulder blades. For these symptoms, his physician prescribed a cathartic, which promptly relieved the abdominal pain. Nevertheless, his extreme weakness and obstipation persisted. Another physician elicited, among other symptoms, the history of pains in both knee joints, which had persisted for a period of ten years. These pains were more severe at night, so that the patient could not cross his knees in bed, and was compelled to assume unusual postures to avoid pain. For this symptom the physician prescribed cinchophen, 5 grains three times daily, over a period of one week. The patient received a statement from the physician mentioning the name and dosage of the drug, in order that it might not be further prescribed by any other physician whom he might consult.

Soon after taking this medication, the patient developed intermittent, generalized itching without any visible skin rash. One week after the use of this drug, and almost five weeks after the onset of his illness, the patient developed jaundice, and light-colored stools. These symptoms brought him first to the Out-Patient Medical Clinic, and then to the hospital ward.

*Examination.* The patient was found to be deeply jaundiced on admission. There were no scratch marks on the skin. The liver and spleen were not palpable. The urine was darkly colored. The stool was greenish-brown.

On the fourth day after admission, the spleen became palpable and definitely enlarged. The stool continued to remain dark green. The temperature was normal throughout, except for a few days when the patient suffered from an acute pharyngitis.

*Laboratory Data.* On admission, the urine was found to contain large amounts of bilirubin. The urobilinogen content varied in dilutions between 1 to 2 and 1 to 40 on different days. The stool at all times was greenish-brown or brown. The guaiac test was negative for occult blood. The hemoglobin was 94 per cent on admission and 82 per cent three weeks later. Examination of the blood showed the presence of 4,000 leukocytes per cubic millimeter. The differential count was:

polymorphonuclear neutrophils, 46 per cent; lymphocytes, 43 per cent; monocytes, 8 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent. After a period of three weeks, the differential leukocyte count became normal and the total leukocyte count, 7,400 cells per cubic millimeter. The heterophile antibody reaction was negative. The erythrocytes failed to sediment at the end of 180 minutes (Linzenmeyer method).

Liver function and other diagnostic tests were performed. Repeated galactose tolerance tests indicated pathological galactosuria; 3.99, 4.50, 6.33, 4.11, and 5.17 gm., respectively. The hippuric acid synthesis test, performed according to the Quick technic, yielded a normal result, 5.3 gm. of benzoic acid. The total cholesterol content and ester partition in the blood was followed throughout the disease. The initial hypercholesteremia, total 355, ester fraction 190 mg. per 100 cc., declined to totals of 250 and 250 and esters of 140 and 165 respectively, after two weeks, and to a total of 275, ester, 135, mg. per 100 cc., after a month. The icterus index in the blood (acetone method) declined from an initial level of 27 to 15 at the end of three weeks, and to 6 just before discharge from the hospital. The bilirubin content of the blood on admission was 4.5 mg. per cent per 100 cc. The van den Bergh reaction was positive. The blood urea nitrogen was 7 mg. and the blood sugar 85 mg. per 100 cc. The blood Wassermann reaction was negative. The total plasma proteins remained at levels of 7 and 6.4 per cent with a normal relationship between the albumin and globulin fractions. The urine was twice examined for tyrosine by the author's tyrosinase method, with negative results.

X-ray examination of the knee joints revealed no evidence of arthritis.

*Course.* The patient was promptly placed on a maximum carbohydrate diet. For a fortnight he appeared to make very little progress, his weakness remaining unchanged and the intensity of his jaundice varying only slightly. The patient noted from the very outset of his jaundice that he was completely free of the pains in his knee joints with which he had suffered persistently over a period of ten years. Soon the intensity of the jaundice began to subside, his appetite improved, and after a period of six weeks, he was practically free of jaundice. It was noted, too, that with the disappearance of the jaundice the joint pains returned. The size of the spleen returned to normal. During his stay in the hospital the patient exhibited an unusual hypersensitivity to Gynergen. An injection of one-half milligram of ergotamine tartrate, administered subcutaneously for the relief of his pruritis (1), promptly produced precordial pain and pains in his limbs. This medication was therefore discontinued.

#### COMMENT

The diagnosis presented no difficulty. The presence of bile in the stool, a marked galactosuria, and the development of splenic enlargement under observation established the diagnosis of intrahepatic jaundice.

The association of arthritis with jaundice was already noted by Graves (2). Out of 208 cases of parenchymatous liver degeneration seen in this hospital since 1909, thirty patients (14%) had had arthritis or severe arthralgia (3). Of the latter, ten (33%) had received cinchophen or its derivatives, while twenty had received none. The association of sciatic neuritis with liver disease has recently been stressed by the author (4). Five cases were reported with pain in the region of the distribution of the sciatic nerve, preceding the development of jaundice for periods lasting from three weeks to two years. In three of these cases, cinchophen was



not administered. The possibility was suggested that the same endogenous or exogenous toxic agents which affect the peripheral nerves may also eventually injure the liver, producing jaundice. The administration of cinchophen thus may act as an accessory toxic factor in individuals hypersensitive to this medication. One toxic agent may render the liver more vulnerable to another.

The analgesic effect of the jaundice state upon joint pains has recently been emphasized by Hench (5). It was already known to Still (6) that certain accidental complications, such as measles, scarlet fever, and catarrhal jaundice, produced distinct improvement in joint symptoms. This phenomenon has now been confirmed by several writers. It has also been noted that upon the disappearance of the jaundice, the joint pains may recur. Hench (7) and others have attempted, but with limited success thus far, to elucidate and reproduce the mechanism whereby the jaundice state produces a physiological reaction which is antagonistic to the continuation of the active symptoms of rheumatoid arthritis. In some mysterious, still unexplained fashion, the abnormal elements produced by jaundice correct or modify the factors causing the joint pains.

The symptomatology in this patient suggests that a disturbance had already existed in the liver for several weeks prior to the ingestion of the cinchophen. In our experience marked anorexia, obstipation, and extreme asthenia occur commonly as symptoms of intrahepatic jaundice.

This case also stresses a significant feature in eliciting the anamnesis in certain patients. For the first few days after admission, repeated queries as to exposure to toxic agents of one form or another met with no result. However, a few days later, after the patient had adjusted himself completely to his new environment, he was able to recall the fact that he had taken medication for his joint pains and that he also had received a written statement from his physician to that effect. The anamnesis cannot be considered complete until several days after admission, when a definitive history may be obtained, after the patient's anxiety over his physical condition has waned and his memory for important details in his illness has been refreshed.

Is there a "safe method" for the administration of cinchophen? This case emphasizes the point that, despite caution on the part of the physician, who was fully aware of the possible hepatotoxic action of cinchophen, the patient developed jaundice. The question whether or not the jaundice can be directly ascribed to the cinchophen, cannot be answered. Moreover, it is not predictable at present whether any particular individual is hypersensitive to the drug or whether some chronic infection or intoxication which has produced the joint pains or the irritation of the sciatic nerve for the relief of which the drug is given, has not already damaged the liver. The cinchophen, which is usually non-toxic, may under these circumstances act as an accessory injurious factor.

## SUMMARY

A case of toxic hepatitis is presented in which cinchophen was administered in therapeutic doses for a week for the relief of long-standing joint pains. The importance of careful history-taking in uncovering etiological factors in patients with jaundice, is emphasized.

The analgesic effect of the jaundiced state upon joint pains is confirmed.

It is concluded that there is at present no "safe method" of prescribing cinchophen. Individual hypersensitivity to this drug is not predictable. Furthermore, in certain patients, previous long-standing infection or intoxication, which is responsible for joint pains or a sciatic syndrome, may already have produced latent liver damage. Cinchophen, which is ordinarily non-toxic, may under these circumstances act as an additional injurious agent.

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# OTITIC STREPTOCOCCUS MENINGITIS WITH RECOVERY

## CASE REPORT

HARRY ROSENWASSER, M.D.

[From the Otologic Service of Dr. J. L. Maybaum]

A number of years ago the presentation of a cured case of otitic *Streptococcus hemolyticus* meningitis would have been read with considerable interest. However, with the advent of sulfanilamide, a powerful therapeutic weapon has been found to combat this dreaded complication. A case of cured otitic bacterial meningitis is here presented to illustrate a number of features which are important in the surgical and chemotherapeutic treatment of this condition.

## CASE REPORT

*History* (Adm. 421480). The patient, a well-nourished 13 year old girl, entered the hospital on March 16, 1938. The history was obtained from her mother, as the patient was drowsy and unresponsive. Three weeks before admission the patient had an acute upper respiratory infection and a few days later developed fever and pain in the right ear. A myringotomy was performed and pus was obtained. Since that time, there had been a profuse discharge. Pain in the ear and fever, varying daily from 101°-103°F., persisted and six days before her admission the patient passed through a severe chill, with the temperature rising to 106°F. She vomited, became extremely dizzy, and seemed to have become "quite deaf." Subsequently the temperature remained elevated, rising daily to 103°F.

*Examination.* The patient was well-nourished, acutely ill, drowsy, irrational, but could be roused. There was a bilateral external rectus palsy. There was some nystagmus present on looking to the left and right, but no vertical nystagmus. The neck was rigid and there were positive Kernig and Brudzinski signs. The knee jerks were absent. A pulsating purulent discharge from the middle ear was present and the mastoid antrum was tender to moderate pressure.

*Laboratory Data.* Hemoglobin was 78 per cent; white blood cells, 17,500 (polymorphonuclear leucocytes, 90 per cent; lymphocytes, 10 per cent). X-ray examinations of the mastoids and petrous pyramids revealed cloudiness of the right mastoid and right petrous pyramid, but no evidence of a destructive process. Lumbar puncture revealed cloudy cerebrospinal fluid under increased pressure, containing 7,200 cells; polymorphonuclear leucocytes, 90 per cent; lymphocytes, 10 per cent. There were no organisms found on smear. A specimen of the fluid was sent to the bacteriologic laboratory for examination and culture. Caloric test indicated that vestibular function was present.

*Operation.* Three hours after admission, the patient underwent an exploratory operation, and a simple complete mastoidectomy was promptly performed. There was extensive softening in the initial groove with a small amount of pus present. After the mastoidectomy was completed, the squama was widely removed, facilitating thorough exposure of the superior surface of the petrous pyramid, according

to the Eagelton technique. No gross pathway of infection was found. A large flat piece of rubber dam with iodoform gauze were placed between the superior surface

TABLE I

DATE (1938)	DOSAGE	CONCENTRATION IN BLOOD	CEREBROSPINAL FLUID			BLOOD—HEMOGLOBIN
			Bacteriology	Cell Count		
				Total	Polys	
		mg. per 100 cc.			per cent	
March 16	Prontosil: 10 cc.		Strep. hemolyt.	7,200	90	
17	10 cc.		Strep. hemolyt.	4,200	90	
18	10 cc.		No growth	750	70	
19	Sulfanilamide: 50 gr.	6.7		1,200	70	60
20	50 gr.					
21	60 gr.	9.5	No growth	420	40	71
22	50 gr.		No growth	380	75	
23	50 gr.	6.7	No growth	300	70	70
24	60 gr.		No growth	800	80	
25	57½ gr.	4.5	Strep. hemolyt.	180	80	
26	45 gr.					
27	52½ gr.		Strep. hemolyt.	1,400	35	
				2,800	95	
28	90 gr.		Strep. hemolyt.			
29	140 gr.	6.3	Strep. hemolyt.	1,400	90	64
30	170 gr.	8.7	Strep. hemolyt.	1,600	90	55
31	200 gr.	10.5	Strep. hemolyt.	1,500	95	65
April 1	200 gr.	9.72	Strep. hemolyt.	4,000	90	69
2	250 gr.	12.1	Strep. hemolyt.	4,600		69
3	280 gr.	13.3	Strep. hemolyt.	2,750	95	
4	280 gr.	13.3	No growth	2,500	85	68
5	280 gr.	9.1	No growth	2,400		59
6	280 gr.		No growth	650	90	
7	280 gr.		No growth	260	95	68
8	265			*	*	68
9	215 gr.	21.5				72
10	200 gr.					
11	200 gr.	16.7				79
12	150 gr.	12.5				
13	150 gr.		No growth	100	50	
14	150 gr.					
15	150 gr.		No growth	50	75	
16	150 gr.		No growth			

\* Only few drops of fluid obtained.

From April 17 through May 4, the drug was administered in decreasing quantities from 150 gr. down to 22½ gr. per day. There was no growth in the cerebrospinal fluid and the hemoglobin was maintained at 70%.

of the petrous pyramid and the middle fossa dura. During the operation the patient was given prontosil 8 per cent, intravenously.

*Course.* The culture of the cerebrospinal fluid obtained before operation was



reported positive for *Streptococcus hemolyticus* beta, as was the pus from the middle ear and mastoid. As soon as the patient reacted after the operation, she was given a blood transfusion, and intensive sulfanilamide therapy was instituted. With the experiences of Perrin Long in mind, the endeavor was made to maintain the concentration of this drug in the blood at approximately 15 mg. per 100 cc. In order to accomplish this, the patient, only 13 years old, received as much as 290 grains of the drug per day. Whenever blood studies, which were performed daily, indicated it, the patient was given transfusions of citrated whole blood. The cerebrospinal fluid, which had become free of bacteria two days after operation, again became positive for *Streptococcus hemolyticus* seven days later and on March 28, 1938, twelve days after the original operation, the petrous pyramid was re-explored in a search for a possible undrained bone focus but none was found.

This patient was treated with sulfanilamide from March 16 until May 4, 1938. During that interval the cerebrospinal fluid, which was examined repeatedly, contained *Streptococcus hemolyticus* beta for the first two days. It then became sterile until at one time, when the dosage was cut down to 45 mg. per day, there appeared an abrupt increase in the cells in the cerebrospinal fluid which rose from 180 to 2,800, with streptococci again being present. This served as a warning, indicating the need for a larger dosage of sulfanilamide for a longer period. Table I graphically indicates the clinical course. The patient responded favorably and at the end of seven weeks of intensive treatment was discharged, well, with no sequelae resulting from the prolonged meningitis and the treatment. Follow-up, eight months later corroborated these observations and also revealed a normal middle ear with excellent hearing.

#### COMMENT

Two significant clinical criteria, demonstrated by this case, are to be emphasized. One is the absolute necessity of knowing pre-operatively whether vestibular function is present. When, as in this case, it becomes evident that a reacting functioning labyrinth is present, the possibility that the meningitis is labyrinthal in origin can be more or less safely ruled out. The clinical events in this case, characterized by the recovery of normal cochlear and vestibular function, justify the course followed. The other significant clinical criterion is based upon the recurrence of all the meningeal signs and symptoms with the appearance of organisms on smear and culture when the dosage of sulfanilamide was suddenly decreased. It obviously indicates the need and the advisability for maintaining an adequate dosage of the drug, even beyond the time when it is reasonable to assume that there is no bacterial activity.

## CLINICAL NEUROPATHOLOGICAL CONFERENCE

*Monday, February 13, 1939*

JOSEPH H. GLOBUS, M.D., *presiding*

*Case 1. Transitional Glioma; left temporal, lobar*

*(From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen)*

*History* (Adm. 411194; P.M. 10455). A man, aged 49, was subject to headaches for many years and was continually taking aspirin with some relief. Aside from an operation at the age of 29 years for a rectal fistula, he was otherwise well until one month before his admission to the hospital, when he suddenly awoke with an unusually severe headache. It was localized to the left forehead, radiating to the left eye, and was unrelieved by aspirin. The headache continued and with it the patient would tire easily. At the end of two weeks he began to display mental changes; he misidentified objects and persons and his memory became defective. At the same time his appetite became poor and he lost weight. He entered the hospital on July 8, 1937.

*Examination.* The patient was alternately apathetic, euphoric, and facetious. At times he was confused and at other times quite lucid. He had difficulty in naming objects; he perseverated and employed round-about expressions to make himself understood. His blood pressure was 116 systolic and 78 diastolic. His pulse rate was 62 per minute.

*Neurological Status.* The right pupil was larger than the left; both pupils reacted poorly to light, the right more sluggishly than the left. The discs were hyperemic and blurred at the temporal margins. There was a suggestive right mimetic facial weakness. The deep tendon reflexes were active and equal. The plantar response on the right was poor. The abdominal reflexes were depressed and readily exhaustible. The extended right upper limb tended to drift from position. The sensory examination could not be evaluated.

*Laboratory Data.* The cerebrospinal fluid was under an initial pressure of 140 mm. of water, contained 28 lymphocytes per cubic millimeter, and was clear and colorless. Total protein, 93 mg. per cent; chlorides, 750 mg. per cent as sodium chloride; sugar, 75 mg. per cent. The Pandy test was three plus. The colloidal gold test was reported as plus-minus. The globulin test was negative, as were the Wassermann tests of both the blood and the cerebrospinal fluid. Hemoglobin, 82 per cent; red blood cells, 3,780,000. The white blood cell count was normal. An X-ray examination of the chest was reported as showing increased density in the markings at the base of the right lower lobe. This was considered to be due in part to an interstitial pneumonitis. The heart showed a moderate degree of concentric hypertrophy of the left ventricle. An electrocardiogram did not indicate any myocardial involvement.

*Course.* On the second day in the hospital his neck was found to be moderately rigid and the Kernig sign much more pronounced. The abdominal reflexes could not be obtained. On that day (July 10) a ventriculography was performed. The left posterior horn did not fill, and the rest of the ventricular system showed a displacement to the right. The anterior horn of the right lateral ventricle seemed moderately dilated and displayed an extremely marked shift to the right of the midline. The fourth ventricle could not be made out with certainty, while the remaining parts of the ventricular system were normal in size.

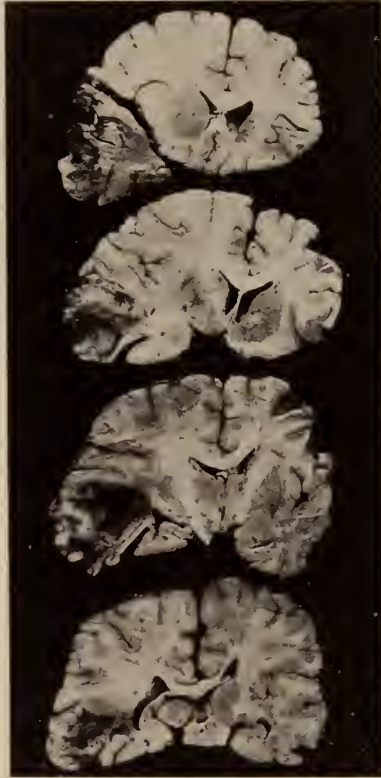


FIG. 1 (Case 1). Coronal sections of the brain showing the tumor occupying the whole of the left temporal lobe. The homolateral ventricle is compressed; the entire ventricular system is displaced to the opposite side.

Following the ventriculography the patient became somnolent and incontinent. His temperature rose and remained for a few hours at 102°F.; his pulse slowed to 48 per minute and continued to be below 60 per minute. An expanding lesion in the left fronto-temporal region was diagnosed and a primary or metastatic neoplasm, tuberculoma, or subdural hematoma were considered as possibilities. Two days after the ventriculography (July 12), a craniotomy was performed, a tumor was found in the left frontoparietal lobe, and a large portion of the tumor was said to have been removed. Following the operation, the patient showed a moderate right-sided paresis; he remained incontinent and spoke rarely, although he seemed to be brighter. Within a few days, the right-sided weakness diminished and the patient

began to speak in sentences. A low-grade spiking temperature continued. Cough and cyanosis set in. An X-ray examination of the chest showed a right-sided bronchopneumonia. The patient became drowsy; the right-sided weakness increased.

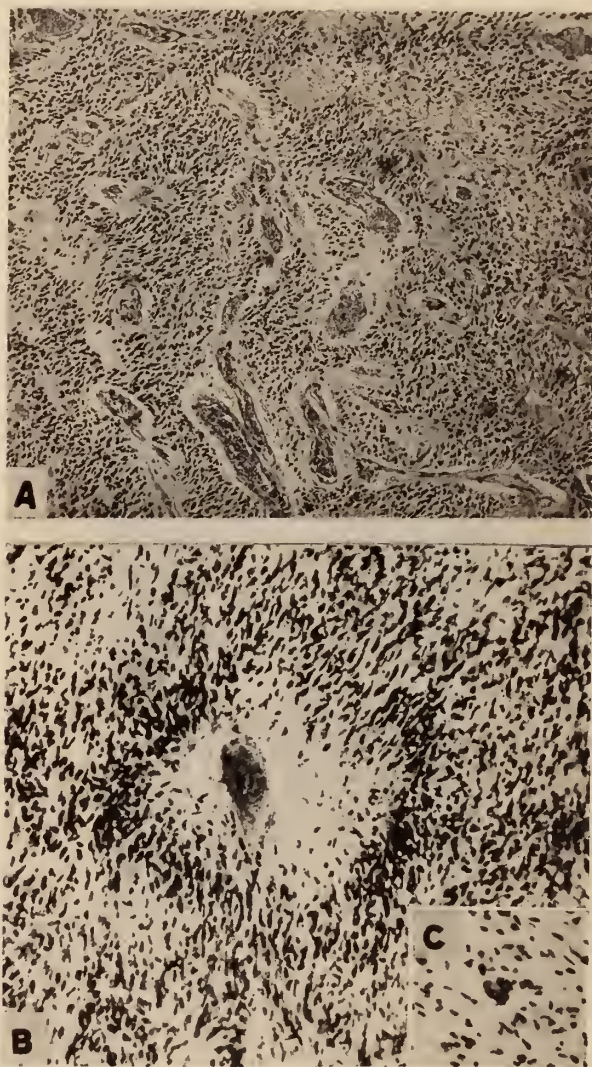


FIG. 2 (Case 1). A. Photomicrograph illustrating structure of the tumor tissue. (Hematoxylin-eosin, 115  $\times$ ). B. Tumor tissue showing palisading of nuclei about a blood vessel (Nissl, 190  $\times$ ). C. A multinucleated giant cell in the tumor tissue (Nissl, 80  $\times$ ).

On July 25, seventeen days after admission, his temperature rose to 105.6°F., and the following day to 107.1°F. He died on July 26, fourteen days after the operation.

*Necropsy Findings. Brain. Gross.* The left cerebral hemisphere was larger than the right. There was a large tumor mass in the left temporal lobe. It en-



eroached on the fissure of Sylvius and caused marked flattening and softening of the surrounding cerebral convolutions. It caused displacement of the cerebral peduncles, mammillary bodies, and optic tracts to the right. The blood vessels at the base were moderately arteriosclerotic.

On sectioning, the entire temporal lobe was found to be occupied by the tumor (fig. 1), which was distinctly demarcated from the adjacent tissue by its dark brownish-red discoloration. The lateral ventricle on the side of the tumor was compressed. Both lateral ventricles were displaced to the right side.

*Microscopic.* Sections of the tumor stained with hematoxylin and eosin showed it to be rich in cells and vessels. The cells were fusiform in outline and were arranged in streams which seemed to be swerving in and out among the many blood vessels (fig. 2A). Palisading of nuclei was found both about some of the blood vessels (fig. 2B) and about cyst-like spaces. Giant cells containing three or four large vesicular or dark-staining nuclei (fig. 2C) were present in small numbers. There were also occasional areas of necrosis. The blood vessels walls were thickened and some vessels contained thrombi. Red blood cells were frequently seen lying free in necrotic areas.

*Comment (Dr. Globus).* When the clinical history in this case is reviewed, two striking features appear in the foreground: the long history of headaches and the apparently precipitate onset of the fatal course of events. On the other hand, a study of the anatomical character of the tumor reveals its exceedingly large size (it occupied almost the entire temporal and part of the occipital lobes) and its histologic structure, that of a transitional glioma. It is rather significant that this variety of primary neuroectodermal brain tumor is likely to be either a large single neoplasm, or consist of several islands spread over a large cerebral territory. This would seem to add support to the probability that this variety of glioma may have its existence in the affected brain for a long time, remaining stationary or progressing slowly in its development and then suddenly, almost explosively, begin to grow rapidly (1). This change in its tempo is marked by the acute onset of neurologic manifestations.

Not without significance are the paucity of localizing signs and the absence of signs of a frankly increased intracranial tension, a condition frequently encountered in this type of cerebral neoplasm (2).

Reported by B. H. Schaffner, M.D.

### Case 2. Neurospongioblastoma; right temporal lobe

(From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen)

*History* (Adm. 399980; P.M. 10121). The patient had had his left kidney removed because of a perirenal abscess at the age of 22. At 49, he had had a left-sided pneumonia; two years later, at the age of 51, his left patella was fractured. In 1935, at the age of 57, he suffered a somewhat vaguely described head injury which was not followed by any un-

toward symptoms. In September 1936, at the age of 58, and six weeks before admission to the hospital, he noticed persistent hoarseness of his voice, and suddenly, four weeks later (October 1936), he began to experience recurrent headaches over the right frontal region (not relieved by aspirin). At this time he noticed that his legs were weak and that he felt persistently sleepy. During the last week of his illness he awoke one morning and, for a short period of time, did not recognize his daughter. Several days before his admission to the hospital (October 20, 1936) he had three spells of vomiting.

*Examination.* The patient appeared undernourished. He seemed confused, yawned frequently, and was kept awake only by constant prodding. He walked unsteadily on a wide base with a tendency to fall backward. He dragged his left leg. The fingers of his left hand moved involuntarily in an athetoid manner. The right side of his skull was very tender to percussion. His left pupil was larger than the right. Both pupils reacted sluggishly but equally to light and in accommodation. The right eye tended to deviate to the right side. A left homonymous hemianopia was found on gross testing of his visual fields. The fundi were normal. A left central facial paresis was present with a wider left palpebral fissure. There was a complete left hemiparesis with some weakness of flexion at the right ankle. The deep tendon reflexes in the upper extremities were more active on the left side. In the lower extremities the right knee kick was brisker than the left; the left suprapatellar and left Achilles tendon jerks were absent. The Babinski sign was positive on the left side; on the right, it was equivocal. The abdominal reflexes were diminished on the left. There was a diminution in all forms of sensation on the left side, most marked in the lower limb.

The patient's blood pressure was 118 systolic and 70 diastolic. His pulse was 64 per minute. His skin showed a scattered vitiligo. A mass, believed to be hemangiomatic, was found on the anterior surface of his left vocal cord. This, in the opinion of the laryngologist, could account for the hoarseness of his voice. His chest was emphysematous with râles at the right apex. A systolic murmur was heard, localized at the apex of the heart. A scar was present on his left flank, the site of his nephrectomy. A pilonidal sinus and cyst were also found.

*Mental Status.* The patient seemed perplexed and markedly confused. He was sociable and polite but did not speak spontaneously. He was careless about his person and would wander aimlessly about without regard for his falling pajamas and consequent exposure. Attention was usually poorly maintained and extensive thinking was impossible. He was generally elated, often attempting feebly facetious remarks, but at other times he was irritable or worried. He answered questions promptly and to the point. Casual conversation was surprisingly good. He was well-oriented in all spheres. Memory tests, as well as simple problems, were well-performed. Calculations and problems involving higher psychic elaboration were poorly done.

*Laboratory Data.* Urine and blood examinations, including the Wassermann test, were negative. The cerebrospinal fluid was under an initial pressure of 86 mm. of water. It contained a total protein of 150 mg. per cent. The Pandy was 3 plus. Perimetry revealed a complete left homonymous hemianopia without sparing of central vision on the left. Caloric tests resulted in exaggerated responses. X-ray examinations of the skull showed an irregular mottling of the bones of the skull with thickening in the post-occipital region. These changes were considered indicative of an early Paget's disease. An X-ray examination of the chest was reported negative.

*Course.* During the patient's stay in the hospital, the right pupil was occasionally found to be larger than the left. The right Achilles tendon reflex disappeared. The knee jerks became equal. The right Babinski sign became positive. His pulse rate varied from 60 to 68 a minute. A subdural hematoma was considered but the presence of hemianopia and hemi-hypesthesia favored the diagnosis of a neoplasm. Primary sources of possible metastasis having been excluded, the brain tumor was finally diagnosed to be a primary one. As to its localization, it was the unanimous opinion that the tumor was deep-seated in the right temporal lobe.

A marked symptomatic improvement in the patient's condition occurred on October 26, six days after admission. He became alert and did not complain of

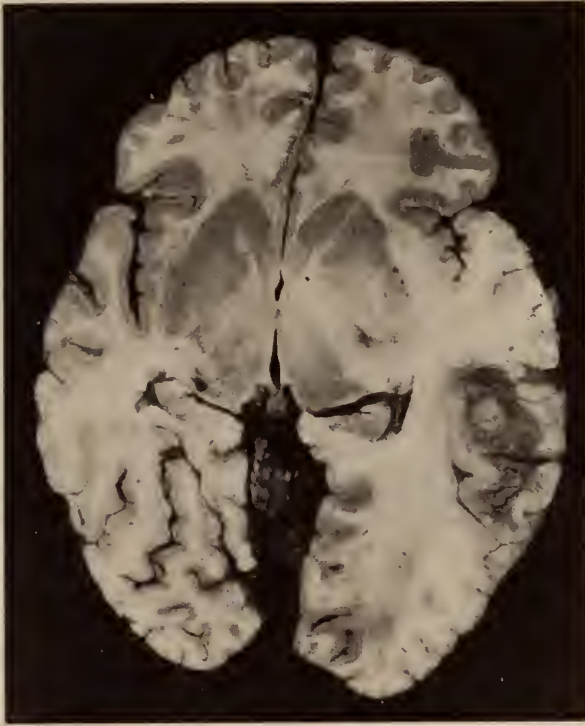


FIG. 3 (Case 2). The tumor is in the right temporal lobe

headache. However, the visual defect persisted. On October 29, a ventriculography was performed. While burr holes were being made, it was observed that the skull bone was gritty and small fragments were sent to the pathological laboratory for study. The exposed dura, though normal in color, did not pulsate. The patient was restless and uncooperative during the procedure, then became drowsy. His pulse remained slow. X-ray examinations of the skull disclosed no air. The fragments of bone removed were reported as showing mosaic figures similar to those found in Paget's disease.

On October 31, the ventriculography was repeated. During the operation the patient was very restless and his pulse rose to 146 per minute, despite minimal blood loss. X-ray studies again failed to reveal the presence of air. In the evening the patient was found to be confused. The left-sided motor and sensory signs became



more pronounced. It was felt that another ventriculographic study would completely demoralize the patient and operation was decided upon. On November 2, a craniotomy was attempted. The cranial bone was found to be thick, soft, and very vascular. Suddenly during the boring of the burr holes an extremely free flow of blood was encountered and the operation had to be terminated without turning down the bone flap. The patient began to recover consciousness in the evening but the next day he sank into a restless stupor and his temperature rose to 102°F. A lumbar puncture produced pink fluid at a pressure of 140 mm. of water. On November 4, because of the patient's failing condition and persistent stupor, it was decided to re-explore the operative site. Some fresh bleeding occurred but no blood could be washed out from beneath the outlined bone flap. His pulse, temperature, and respirations remained elevated. He died on November 5, 1936.

*Necropsy Findings. Brain. Gross.* The right cerebral hemisphere was enlarged; the markings of the right temporal lobe were partially obliterated, especially posteriorly, where it felt nodular and presented a red mottled appearance.

On sectioning, the posterior part of the temporal lobe disclosed a circumscribed area of a somewhat greenish-yellow color, encircled by a slightly brownish zone. This in turn was surrounded by an area of edema (fig. 3). The ventricles were displaced to the opposite side. A section through the centrum ovale disclosed two hemorrhagic areas, one in the left hemisphere close to the lateral aspect (about 4 cm. from the occipital pole and 4 cm. from the medial border). It measured about one-half a centimeter in diameter and could be traced downward, diminishing in size, until, at about the level of the dorsum of the corpus callosum, it was only three millimeters in diameter. At this level there was another similar hemorrhage near the medial border of the opposite hemisphere. The left hemorrhagic area could be traced further downward, close to the anterior end of the posterior ventricle, down into the pulvinar of the thalamus. These hemorrhagic areas were apparently the results of the attempted ventriculograms.

*Microscopic.* The tumor was found to be very cellular and highly vascular. It contained extensive areas of necrosis. In many areas the cells displayed a uniform distribution, while in others they tended to form small islands, or nests, separated by bundles of fibers. The most dominant cell form was a large oval-shaped cell (fig. 4). The cytoplasm of these cells was abundant and in an iron hematoxylin preparation stained either lightly with a ground glass appearance or more darkly with a granular appearance. The cells contained one or two nuclei which were eccentrically located and often contained a well-defined nucleolus. The cell processes were uniformly fine but some cells gave rise to a single broad process. In some of the cells, a group of fine fibers took origin at one pole of the cell in a tail or mane-like manner. A few cells, somewhat angular in shape, gave rise to three or four broad processes. Several large, star-shaped cells were encountered, one of which showed fibrillae in one of its six processes. In and about the cellular nests and throughout the more uniform parts of the tumor there were many undifferentiated elements, as well as nerve cells, in various stages of differentiation. These last included small round to oval cells, characterized by a pale nucleus and a single nucleolus, and larger pyriform and fusiform cells with similar characteristics. No mature glial forms were seen. In one field there were two bipolar cells, of which one had the features of a cell in the nerve cell series (fig. 5A), while the other with clear cytoplasm and a bean-shaped, stippled nucleus resembled an undifferentiated glia cell (fig. 5B). Cells of this latter type were frequent among the masses of fibers that passed through the tumor. Some bipolar cells occasionally showed two nuclei (fig. 5C). A large tadpole-shaped cell, which presented the features of a nerve cell and gave rise to a broad process at one end and shorter, more delicate processes at other parts, was occasionally encountered (fig. 5D). Nerve cells of triangular



shape but relatively lilliputian in size were also met with. Multinucleated giant cells and mitotic figures were not infrequent.

*Comment* (Dr. Globus). The existence of an expanding intracranial lesion was recognized without difficulty, in spite of the fact that the fundi were normal. But with the rapid onset of the signs and the history of a trauma, the existence of a subdural hematoma had to be considered. In view of the presence of hemianopia and sensory disturbances, however, this type of expanding lesion was considered unlikely. The question

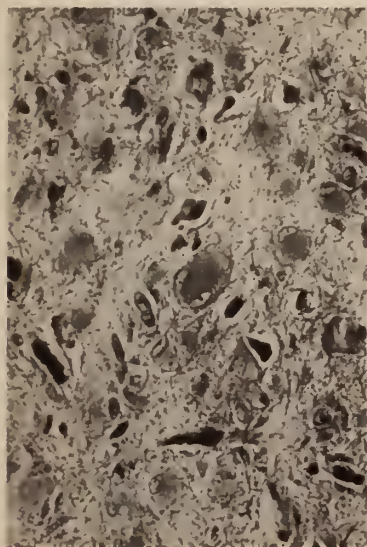


FIG. 4

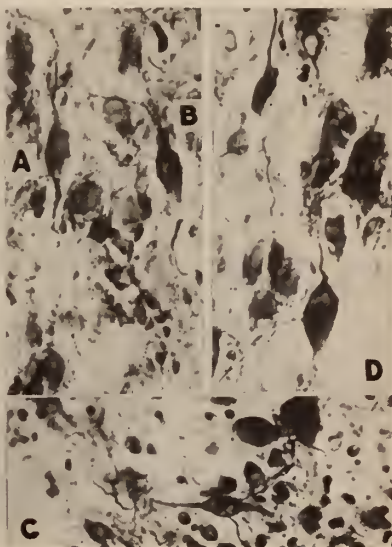


FIG. 5

FIG. 4 (Case 2). Tumor tissue showing the dominant cell form containing a clear nucleus with a well-demarcated nucleolus. Cells of this type containing two nuclei are not infrequent (Iron hematoxylin, 440  $\times$ ).

FIG. 5 (Case 2). Tumor tissue showing two bipolar, fusiform cells, one (A) resembling an undifferentiated glia cell, the other (B) resembling an undifferentiated nerve cell (Hortega I, Globus modification, 560  $\times$ ). C. Tumor tissue showing a binucleated bipolar cell (Hortega I, Globus modification, 550  $\times$ ). D. Tumor tissue showing a large, atypical, tadpole-shaped nerve cell (Bielschowsky, 425  $\times$ ).

arose then as to whether or not the tumor was metastatic in origin; but X-ray examination of the chest and other investigations failed to disclose a primary or metastatic lesion elsewhere. All this pointed to the probability that the neoplasm was primary in the brain.

The neurospongioblastic character of the tumor serves to explain many of the clinical manifestations in this case, such as the abrupt onset, the rapid progress, the lack of papilledema—features which are not infrequent in this form of neoplasm (3).

Reported by J. M. Zucker, M.D.

*Case 3. Neuroepithelioma; right strio-thalamic region*

(From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen)

*History* (Adm. 400803; P.M. 10156). A man, 50 years of age, was for many years subject to headaches, which would recur once a month. He was found to have hypertension at the age of 40, when examined for life insurance. Aside from experiencing pain in the right lower back and right thigh for a number of years, he registered no other complaints until six weeks before admission to the hospital. It was then observed that the left side of his mouth drooped, that particles of food mixed with saliva would drool out of that corner of his mouth, and that his left palpebral fissure seemed to have become smaller than the one on the right. One week later, severe persistent headache set in. It affected the top and the right side of his head. At the same time his left upper limb had become weak and clumsy. The weakness passed off gradually but the clumsiness persisted. By the end of another week the patient began to display mental changes; he would give irrelevant replies to questions and would make lewd remarks which were not in keeping with his previous conduct. The mental alterations progressed so that he gradually lost all sense of time and place. He displayed poor insight into his condition and, in contrast to his attitude before his illness, became more cheerful and more pleasant. Shortly before entering the hospital ward he complained of a peculiar odor which he described as of an "evil" or "medicinal" character.

*Examination* (November 9, 1936). The patient held his head as though in pain. He was pale, apathetic, and inattentive. Constant prodding was required to secure his cooperation. His speech was thick and slurred. He was disoriented and confused. He often laughed without cause and answered some commands with the words, "Why not?" and "What then?"

*Neurological Status.* The right frontal region of the skull was very tender to percussion and gave a duller note than that on the opposite side. There was a slight stiffness of the neck and a bilateral Kernig sign. Papilledema was present in both optic discs but it was greater in the left. Both pupils were small but unequal, the left being larger than the right. They reacted well to light. The left palpebral fissure was larger than the right. There was a tendency for conjugate deviation of the eyes to the right with a weakness of conjugate movement to the left. There was a left supranuclear facial paralysis. The left upper limb was weak and was held flexed across the chest. Test acts were awkwardly performed on the left side. The deep tendon reflexes in the left upper extremity were more active than those on the right side. The knee and ankle jerks were equal. There was a questionable left-sided hypalgesia.

His prostate was enlarged but smooth. His blood pressure was 125 systolic and 78 diastolic; his pulse rate was 62 per minute.

*Laboratory Data.* Cerebrospinal fluid: clear; initial pressure, 140 mm. of water; globulin, one plus; Wassermann test, negative; cells, 8 mononuclears per cubic millimeter; total protein, 77 mg. per cent; chlorides, 705 mg. per cent as sodium chloride. Blood chemistry, total and differential blood counts, blood Wassermann

test, and the urine examination, all negative. X-ray examinations of the skull and chest were reported as negative.

*Course.* The diagnosis of a right cerebral tumor was made with the probable localization in the right frontoparietal lobe. It was thought to be a primary lesion, spongioblastic in nature. On the evening of the patient's first day in the hospital a re-examination showed that the left cremasteric reflex had disappeared and the left abdominals were diminished. The left hemisensory changes were found to include

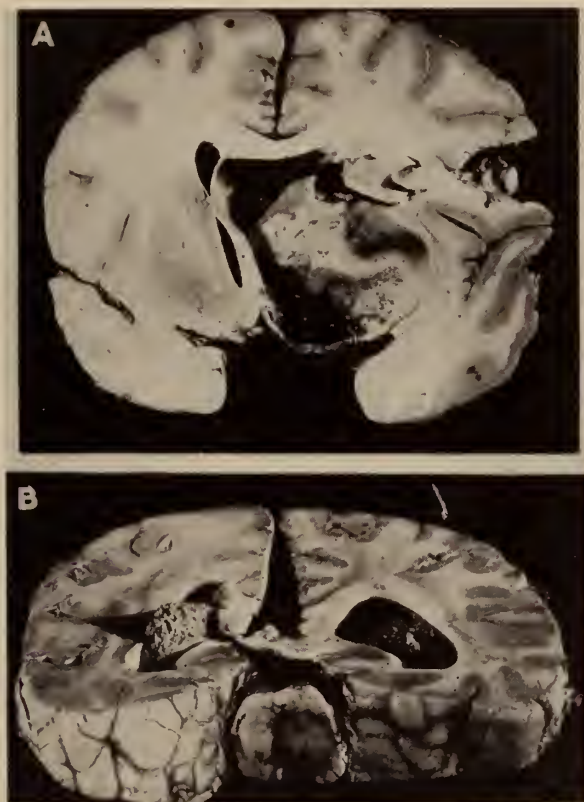


FIG. 6 (Case 3). Coronal sections of the brain: showing (A) the tumor replacing almost the entire corpus striatum and internal capsule on the right side; (B) the extension of the tumor into the tegmentum of the right side of the midbrain. The medial and ventral parts of the midbrain show discoloration due to hemorrhage.

vibratory sense. The following day a hemorrhage appeared in the left optic disc. On the third day in the hospital (November 12) an exploratory craniotomy was performed. A cyst containing about 30 cc. of yellowish fluid was found in the right frontal lobe. The cyst wall consisted of grayish tumor tissue and was not well-demarcated from the neighboring brain tissue. As much as possible of the tumor tissue was removed. Following the operation the patient developed a left hemiparesis. For two weeks his condition remained little changed with an occasional suggestion of improvement. But at the end of this period (November 26) he began to become increasingly drowsy. Nine days later (December 5) he had several left-



sided convulsions and sank into stupor, dying the following day (December 6), three and a half weeks after the operation.

*Necropsy Findings. Brain. Gross.* There was a postoperative cavity, measuring about 3 cm. in diameter, in the parietal lobe of the right cerebral hemisphere. It communicated with the lateral ventricle.

On sectioning, a tumor mass was found projecting into the right lateral ventricle, mainly into its anterior horn. The tumor occupied almost the entire region of the

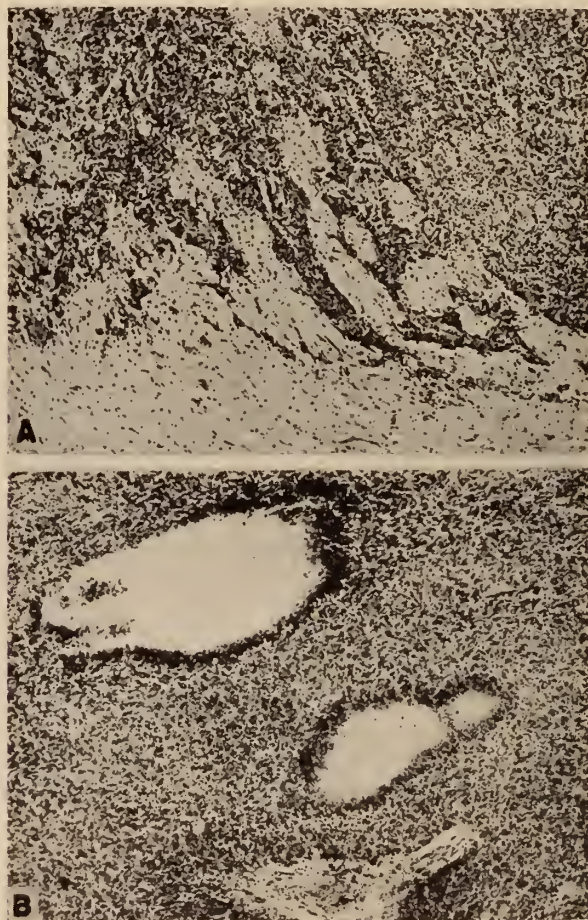


FIG. 7 (Case 3). Photomicrographs showing (A) tumor tissue invading adjacent brain tissue (Hematoxylin-eosin, 90  $\times$ ); (B) tumor tissue containing ependymal cyst-like structures (Nissl, 87  $\times$ ).

corpus striatum and the internal capsule on the right side, being demarcated laterally by the internal capsule (fig. 6A). It measured 3 cm. in the horizontal and 3.5 cm. in the vertical plane. At its lower end it was more or less continuous with a yellowish area of discoloration in the hypothalamic region. From this region it again widened into a rounded mass occupying the right tegmentum of the midbrain. At this point a fairly prominent hemorrhage was found to occupy the medial and



ventral parts of the left half of the midbrain (fig. 6B). This extravasation could be traced caudally to the posterior half of the pons.

*Microscopic.* Sections of the tumor stained with hematoxylin and eosin revealed it to be densely cellular and infiltrating the adjacent brain tissue (fig. 7A). In some areas structures resembling ependymal cysts were present (fig.

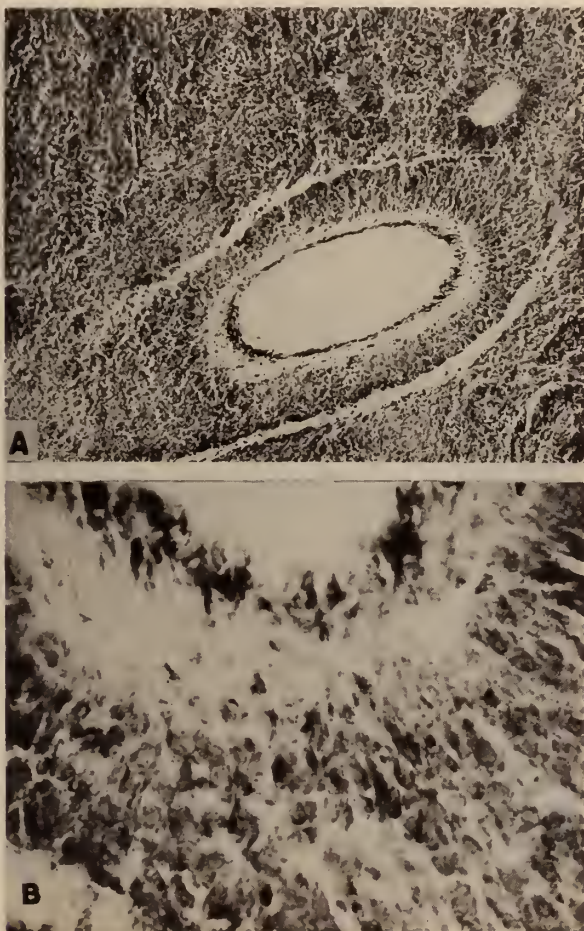


FIG. 8 (Case 3). Photomicrographs showing (A) tumor tissue with the neoplastic cells grouped about a blood vessel (Nissl, 90  $\times$ ). B. Small nerve cells, recognized by their dark coloration, are among the tumor cells about the vessel shown in A (515  $\times$ ).

7B). The tumor cells, containing nuclei darkly stained and variable in size and shape, were of large size and irregular outline. There were numerous giant cells and occasional mitotic figures. Blood vessels were abundant throughout the tumor tissue, their walls showing hypertrophy of the intima with moderate hyalinization of the media and marked proliferation of the adventitia. Scattered through the tumor, and especially in fairly wide cellular zones about blood vessels, there were

found large numbers of oval, pyriform, and triangular cells. They presented a narrow rim of deep-staining cytoplasm surrounding a pale nucleus containing a deeply stained nucleolus (fig. 8 A & B). In some of such cells the cytoplasm contained a number of irregular and deeply staining granules (fig. 9A). Throughout the tumor tissue there were found other fairly well-developed nerve cells occurring

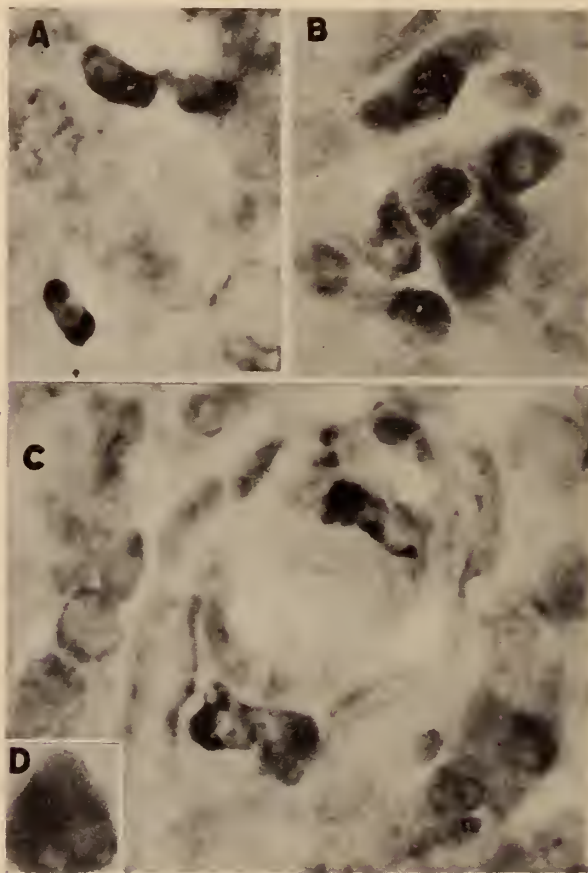


FIG. 9 (Case 3). Photomicrographs showing well-developed nerve cells in the tumor tissue: A. isolated cells with deeply staining cytoplasm, clear nucleus, and well-defined nucleolus (Nissl, 1375  $\times$ ); B. a nest of nerve cells with well-developed tigroid substance (Nissl, 1450  $\times$ ); C. nerve cells hugging a small blood vessel (Nissl, 1375  $\times$ ); D. a cell containing several nuclei, each with a nucleolus (Nissl, oil imm., 1500  $\times$ ).

in nests (fig. 9B) or enveloping smaller vessels (fig. 9C). Some of the cells contained several nuclei, each enclosing a nucleolus (fig. 9D). In the brain tissue adjacent to the tumor there were large areas of extravasation and necrosis. Many compound granular cells and occasional ameboid glia were seen there.

In areas remote from the tumor there was marked thickening of the leptomeninges. The pial blood vessels were engorged and showed swelling, irregularity,

and hyalinization of their medial coats. In both cortex and subcortex there was a considerable increase in glial elements. Beneath the ependyma in some areas there were extensive accumulations of compound granular cells.

A section through the midbrain disclosed a fairly large hemorrhage underneath the aqueduct.

*Comment* (Dr. Globus). The abrupt onset and the rapidly progressive course justifies the grouping of this case with the so-called acute brain tumor (4). This form of tumor is usually found to be of a malignant variety, in the sense that its cellular elements are of a low stage of differentiation. Such is the situation in this case; the cell form is nearest to that of the primitive neuroectoderm (the neuroepithelium) and the cellular arrangement is a primitive one. These two features warrant the allocation of this primary brain tumor with the neuroepithelioma, a tumor form in which all of the neuroectodermal derivatives have retained a very low stage of differentiation.

Reported by *E. P. Mindlin, M.D.*

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## CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, November 2, 1938*

### Pigment Cirrhosis of the Liver; the differentiation from true hemochromatosis

*(From the Medical Service of Dr. B. S. Oppenheimer)*

*History* (Adm. 424434; P.M. 10827). The patient, a Russian Jew, was admitted to the hospital for the first time on May 22, 1938. Thirty years before he had had a penile lesion associated with a urethral discharge, which subsided after one month. Eight years prior to admission he was found to have a systolic blood pressure of 180. At about this time, varicose veins of the lower extremities were also noted and it was observed that his skin was darkening. He subsequently developed a varicose ulcer on the inner aspect of his left leg and began to complain of occasional cramp-like pains in the calves unrelated to exertion. Two years before hospitalization routine examination revealed the presence of glycosuria. During the prohibition era he consumed large quantities of whiskey manufactured in copper stills. His fatal illness began four months before admission, when he noted mild abdominal pain, jaundice, dark urine and light stools. He also began to complain of weakness and bilateral ankle edema. A blood icteric index of 35 and a 2 per cent glycosuria were reported by his physician.

*Examination.* The patient was obese and moderately icteric. There was a diffuse yellow-brown pigmentation of the face, neck and extremities. The pupils were irregular; the left was larger than the right and reacted better to accommodation than to light. A loud systolic murmur was heard at the aortic area transmitted towards the apex. The second aortic sound was louder than the second pulmonic sound. The heart rate was 86 and the rhythm, regular. The blood pressure was 150 systolic and 76 diastolic. The hepatic and splenic edges were palpable at the costal margin. The left epididymis was large and firm and a scar was present on the coronal sulcus of the penis. A few small external hemorrhoids were found. The pretibial skin was a diffusely pigmented mottled bronze with lighter brown spots up to the mid-knee. There was a healing ulcerated area on the inner aspect of the lower leg. Tender varices were noted on both legs.

*Laboratory Data.* Blood hemoglobin was 81 per cent (Sahli). The white blood cells numbered 6,000 per cu.mm. with a normal differential count. X-ray examination of chest and abdomen was not revealing. The electrocardiogram showed changes suggestive of ventricular disease. The blood chemistry findings were as



follows: urea nitrogen, 11 mg. per cent; cholesterol, 390 mg. per cent; icteric index, 30; bilirubin, 4 mg.; total protein, 6.4 per cent. The blood Wassermann and Kahn tests were both negative. The urine showed no bile at any time and the urobilin varied from 1:80 to 1:1280, and occasional faint traces of sugar were noted. No urinary melanin or tyrosine were found. During the Janney test for sugar tolerance, the blood sugar rose to a high level of 290 mg. per 100 cc. The galactose tolerance test suggested the presence of liver disease, a total excretion of 8.6 gm. being observed. The stools were guaiac negative and showed a trace of urobilin.

*Course.* Skin biopsies were obtained from the neck and leg and the presence of hemosiderin in the corium and subpapillary zones demonstrated slight amounts of the iron pigment in the neck, large amounts in the skin of the leg. After a week in the hospital, the icteric index fell to 21. Eleven days after admission the patient's internal hemorrhoidal vessels became thrombosed and painful. The rectum was accordingly dilated in the operating room under an ethylene anesthesia which lasted but a few minutes. During the next twenty-four hours his condition went quickly downhill; his pulse and respiration were rapid. Suppression of breath sounds and rales were heard at the right base. He died in coma.

*Necropsy Findings.* The liver was slightly shrunken and showed the typical hobnail appearance of Laennec's cirrhosis. Large amounts of hemosiderin pigment were present in the hepatic nodules, mainly within the liver cells, but with smaller amounts in the Kupffer cells. The pancreas was slightly increased in consistency; hemosiderin pigmentation of the acinar cells but no increase in connective tissue was noted. The spleen weighed 300 grams and was moderately pigmented. The bone marrow showed evidence of hyperplasia.

*Comment.* *Dr. Klemperer:* The case presented does not belong to the group of hemochromatosis. The pigmentation of hemochromatosis was due to two varieties of pigment: 1) hemosiderin, an iron containing pigment which is found mainly in epithelial structures and in the skin about the sweat glands; 2) hemofuchsin, a non-iron containing pigment found, for the most part, in smooth muscle cells and fibroblasts. In the case under consideration, only hemosiderin could be demonstrated. This patient had Laennec's cirrhosis, coincidental diabetes and hemosiderosis, which may have been secondary to chronic blood destruction.

*Dr. Baehr:* The hemofuchsin seen in the tissues in true hemochromatosis is derived from blood pigment and so is the hemosiderin in this case. Both types of cirrhosis should be grouped under the one general heading of pigment cirrhosis. Both conditions result in cirrhosis of the liver and of the pancreas. The theory of Mallory that pigment cirrhosis may be due to copper poisoning resulting from imbibing of alcoholic beverages distilled from copper vessels has not been confirmed.

*Dr. Klemperer:* The skin in general hemochromatosis shows the presence of iron-free pigment in the upper corium associated with abundant iron pigment in the deeper corium about the sweat glands. But cases of hemochromatosis may lack any significant pigment deposits. The diagnosis of hemochromatosis, therefore, must not depend upon the skin biopsy.

## Hodgkin's Disease

(From the Medical Service of Dr. George Baehr)

*History* (Adm. 384459; P.M. 10798). The patient, a twenty-eight year old Jewess, was admitted to the hospital for the first time on September 9, 1935 with a complaint of cervical glandular enlargement of one year's duration. For several months, she had had cramp-like lower abdominal pain. Twenty-six years previously, at the age of two, an appendectomy was done. On admission, enlarged nodes were felt in the neck and axillae. A biopsy of a cervical node disclosed the presence of Hodgkin's disease. Laboratory data at that time were essentially negative except for a white cell count of 15,400 cells per cu. mm. with 67 per cent polymorphonuclear neutrophils and 4 per cent eosinophiles. X-ray examination of the chest revealed enlarged paratracheal lymph nodes. She was discharged from the hospital and in the interval before her re-admission, she received intensive X-ray therapy. She was well until five days before her second admission on April 27, 1938. At that time nausea, vomiting and abdominal distention appeared, against which enemata were ineffectual. The patient apparently had an intestinal obstruction and was readmitted to the hospital.

*Examination.* There was no lymphadenopathy or splenomegaly. The abdomen was tense and distended, and the patient appeared acutely ill.

*Laboratory Data.* The blood hemoglobin was 64 per cent and the red blood count was 4,200,000 per cu. mm. The remaining blood studies were normal. X-ray examination of the abdomen showed a distended small bowel suggestive of intestinal obstruction.

*Course.* The patient was given supportive therapy for one week and then an exploratory laparotomy was performed. Adhesions were found at the old appendectomy site, which had obstructed the ascending colon. An ileo-transverse colostomy was therefore done. Despite the relief of the intestinal obstruction, she gradually grew weaker and died ten days postoperatively.

*Necropsy Findings.* The significant lesions were in the *abdominal lymph nodes* which were moderately, but diffusely enlarged. They showed the typical histology of Hodgkin's disease with marked fibrosis. There was less involvement of the *spleen* and *liver* and localized infiltration of the *lung*.

*Comment.* *Dr. Klemperer:* The post mortem findings of Hodgkin's disease were enough to explain the progressive asthenia and death.

*Dr. Bachr:* The intensive radiotherapy eliminated all the superficial lymph node enlargements and converted a generalized Hodgkin's disease into one that had an almost purely abdominal localization.

## Lymphosarcoma of the Small Intestines

(From the Medical Service of Dr. B. S. Oppenheimer and the Surgical Service of Dr. J. Garlock)

*History* (Adm. 429063; P.M. 10942). The patient, a forty-year old Jewish painter, was admitted to the hospital for the first time on March 2,

1938. For three years before admission, he had had frequent episodes of vomiting and for six months he had noted watery brown stools associated with upper abdominal pain and distention.

*Examination:* The patient was an emaciated male. The heart sounds were distant and the blood pressure was 100 systolic and 70 diastolic. The abdomen was distended and tympanitic. There was fullness and a sense of a mass in the left upper quadrant. There was early clubbing of the fingers and toes.

*Laboratory Data.* The blood hemoglobin was 80 per cent. (Sahli) with a red cell count of 4,700,000 per cu. mm. The white cell count was normal and the stool was one plus positive for occult blood. An X-ray examination of the chest was not revealing. Barium enema, followed by X-ray examination of the colon, showed obstruction of the hepatic flexure. As high as 36 units of free acid were present in the stomach after the injection of histamine. The total blood protein was 5.7; the blood Wassermann test was negative; the urine showed no significant changes.

*Course.* During the two weeks following admission the patient showed increasing signs of intestinal obstruction and he was therefore operated upon. An obstructing peritoneal band, probably of congenital origin, was found at the colonic hepatic flexure and was divided. Colon, stomach and duodenum were then explored and found negative. The patient experienced moderate relief of his symptoms and was discharged after a one month convalescence.

*Second Admission.* The patient was readmitted four weeks after discharge on May 14, 1938 because of progressive weakness, abdominal pain, and diarrhea. Physical examination showed little change except for slightly increased cachexia. The laboratory examinations were essentially unchanged except for the following: the total dried stool fat was 47 per cent and the Janney sugar tolerance test showed an increased tolerance with the highest sugar level at 110 mg. per cent. The duodenal contents contained diastase and trypsin. Gastro-intestinal X-ray examinations demonstrated areas of constriction, serration and dilatation of the small bowel. He was treated intensively with a high vitamin diet, transfusions of blood, and hematopoietic agents with no change in his condition after three months' observation. He was discharged from the hospital only to return again after two weeks, on September 1, 1938, because of severe abdominal cramps.

*Third Admission.* On this admission a definite grapefruit-sized mass, which was firm, nodular, and tender was felt in the lower end of the right rectus scar. A pea-sized nodule was felt on the anterior rectal wall above the prostate. X-ray examination of the small bowel revealed a picture similar to that seen before. Because of the possibility of a lymphoblastomatous disease of the small intestine, radiation therapy was instituted and one week afterwards the mass disappeared. After one month the mass was again noted, concomitant with the appearance of diarrhea. The patient became progressively weaker and he died in coma six weeks after the last admission.

*Necropsy Findings.* There was a diffuse lymphosarcomatous process in the stomach and small intestines. Flat, indurated plaques were seen in the stomach wall. The majority of the mesenteric lymph nodes were moderately enlarged. The lymphosarcomatous involvement was progressively more severe as the terminal ileum was approached. In this area the bowel was diffusely infiltrated and the mesenteric lymph nodes were massive. Rare nodules of lymphosarcoma were found in the liver and kidneys.

*Comment.* Dr. Baehr: The early clinical impression was non-tropical sprue because of the flat Janney sugar curve, the bulky diarrhea, and the increase in stool fat. Unfortunately, these findings may be observed in

any patient with intestinal hyperperistalsis. They are not diagnostic of sprue without hematologic supporting evidence. Furthermore, careful hourly observations of the passage of a barium meal through the small intestine should be made in every case of suspected sprue in order to rule out organic disease of the small intestine, such as regional ileitis, tuberculosis and lymphosarcoma. The lack of response to liver therapy militated strongly against the diagnosis of sprue. The X-ray pictures were characteristic of lymphosarcoma of the small bowel. There were characteristic zones of dilatation of the small bowel with alternating zones of contraction of normal width. The lymphosarcoma grows through the muscularis, destroying it in various sites along the length of the small intestine and this is responsible for the multiple sites of dilatation. It should be emphasized that it is in this disease that early diagnosis is important because of the curative effect of radiation therapy.

Reported by *Abner Kurtin, M.D.*



## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*A Suggested Test for Cortical Adrenal Carcinoma.* R. T. FRANK. J.A.M.A. 109: 1121, October 2, 1937.

In four cases of adrenal cortical carcinoma, the excretion of estrogenic substance was found greatly increased in the presence of a negative pregnancy test. In contradistinction to this, fifteen other cases in which all or some of the symptoms of adrenal cortical syndrome were present, gave a negative reaction. Among these fifteen cases were adrenal cortical adenoma, adrenal hyperplasia, and adrenal medullary paraganglioma. Nor was such high excretion noted in more than five hundred other patients in whom the estrogenic substance was bioassayed. If further confirmation is obtained, this should prove a valuable test for adrenal cortical carcinoma.

*Meningiomas. Origin, Divergence in Structure and Relationship to Contiguous Tissues in Light of Phylogenesis and Ontogenesis of the Meninges, with Suggestion of a Simplified Classification of Meningeal Neoplasms.* J. H. GLOBUS. Arch. Neurol. & Psychiat. 38: 667, October 1937.

In the past many names were assigned to intracranial and intraspinal tumors of meningeal derivation. They were called, at one time or another, psammoma, dural sarcoma, epithelial cancer, fibroblastic tumor, epithelioma, endothelioma, cancer of the arachnoid, etc. Some investigators considered such tumors to be dural in derivation, while others traced their origin to arachnoid embryonal rests or to islands of glial tissue which were supposed to have been displaced into the meninges in the course of the migration of glial elements. This origin from neuroectodermal tissue was stressed by a group of workers who sought to prove that the leptomeninges were derived from the neural crest. Still others thought that partly differentiated cells in the primitive meningeal tissue assumed a neoplastic tendency and so gave rise to tumors which contained, at one time or another, a cell type found in the meningeal anlage. Thus fibroblastic, melanoblastic, osteoblastic and angioblastic varieties were identified. Obviously the recognition of their origin and the adoption of a satisfactory terminology for meningeal tumors stimulated many investigators to find a way out of the existing confusion.

Globus offers a new approach to the problem by employing the known facts concerning the phylogeny and ontogeny of the brain coverings. He points to the accepted observation that the mesenchymal tissue, which fills the space between the skin and neuroectoderm and is intimately connected, on the one hand with the overlying skin and on the other, with the medullary tube, is the early forerunner of all

the brain coverings. This so-called skeletoneural intertissue in the course of its growth and histogenesis splits into several bands of denser tissue. In this manner it gives rise to: 1. the vascular pia mater with its numerous extensions into the brain substance; 2. the arachnoid; 3. the dura mater; and 4. the periosteum lining the internal surface of the cranial bones.

The author bases his conclusions on a study of over one hundred tumors of meningeal derivation. With the cellular changes observed during the normal phylogenesis and ontogenesis of the meninges in mind, he endeavors to correlate these with the structures found in meningeal tumors.

Meningiomata are known to contain bone, collagenous connective tissue, endothelial cells, and blood vessels. This coexistence is now readily explained when it is recalled that the undifferentiated meningeal primordium contains the ingredients essential for the elaboration of these components. These components may exist side by side in one tumor; in another the dural component may predominate; while in either the pial or the arachnoid elements are in greater abundance.

These observations lead the author to suggest the following classification of meningiomata:

1. *Meningioma indifferetiale, or mesenchymatous meningioma.* This tumor duplicates the structure of the mesenchymatous anlage of the meninges.

2. *Meningioma omniforme, or primitive meningioma.* This tumor duplicates all the structures derived from the primitive meninx, which is already in an advanced stage of differentiation. It may contain bone traceable to the periosteal component of the "skeletoneural intertissue", fibrous tissue recalling the structure of the dura, "epithelial" cells duplicating the cells in the arachnoid, and vascular channels in various stages of maturation, denoting a pial origin.

3. *Pachymeningioma, or dural fibroblastoma.* This type contains large interlacing bundles of collagenous fibers, occasionally enveloping solid groups of cells of the epithelial variety. This type of tumor, in which the dura alone is represented, is exceedingly rare. It may in areas present nothing but dural tissue, but on careful search arachnoidal structures will be observed, and possibly some which indicate pial origin. Here remnants of bone are often prominent.

4. *Leptomeningioma, or arachnoid meningioma.* In this type of tumor arachnoidal structures predominate, not, however, to the full exclusion of the pial derivatives.

5. *Meningioma piale; pial of vascular meningioma.* Here vascular structures of various types dominate the histologic pictures, and, in accordance with the degree of maturity and the character of the vascular elements, the pial meningioma is divisible into several subgroups, such as the *hemangio-endotheliomatous*, the *hemangiomatous* and the *psammomatous* subtypes. Occasionally the pial tumor contains many pigment-carrying cells, acquiring a *melanomatous* character; this constitutes another subtype.

6. *Sarcomatous meningioma.* This type of tumor, which cannot be distinguished from sarcoma elsewhere, is closely related by origin and structure to the mesenchymatous and pial forms of meningioma. It assumes the character of either diffuse meningeal sarcomatosis or circumscribed intracerebral sarcoma.

In the case of the so-called medulloblastoma, the author suggests that in some instances this may be a variety of the pial meningiomata, for the following reasons: 1. many of these tumors fail to yield clear-cut evidence of their gliogenous or neuroblastic character when special stains are utilized; 2. careful study reveals areas in which vascular formations are dominant structural features.

T. Meltzer.

*Prophylactic Vaccination Against Intracranial Complications Following Pneumococcus Type III Mastoiditis.* J. L. GOLDMAN AND C. HERSCHBERGER. J.A.M.A. 109: 1254, October 1937.

This paper presents immunological and clinical studies on the value of vaccination in cases of pneumococcus type III acute mastoiditis for the purpose of preventing intracranial complications. Every case of pneumococcus type III acute mastoiditis admitted to the Otological Service of The Mount Sinai Hospital for the past five and one-half years has received an autogenous type III pneumococcus vaccine. A study of the vaccinated cases was made and compared with a series of non-vaccinated cases. Of fifty-six patients who received a full course of vaccine, in only two instances could death be attributed to meningitis which directly complicated a mastoid infection—a mortality rate of 4 per cent. During the ten years prior to this work, forty had mastoiditis due to infection with the type III pneumococcus. Of these, thirteen died of meningitis—a mortality rate of 32.5 per cent. (The mortality rate for the previous five years was 22 per cent.) The possible value of human prophylactic vaccination with pneumococci is well supported by experimental work indicating that animals can be protected from lethal doses of pneumococci by vaccination and can develop type-specific antibodies shortly after administration of the vaccine.

*Some of the Functions of a Psychiatric Department in a General Hospital.* J. KASANIN. Read at the Meeting of the Central Neuro-Psychiatric Association, October 8-9, 1937, Chicago, Ill.

The psychiatric department in a general hospital may have a variety of functions, such as research, undergraduate teaching, therapy, education of the staff, etc. Even if definite contributions can be made in any of these fields, the main function of such a department lies in broadening the scope of psychiatry and demonstrating how it can be applied and correlated with the field of general medicine. The educational aims of a psychiatric department can be best achieved, not by establishment of special psychiatric clinics, but by the psychiatrist working as a member of any one of the general medical or special clinics. There the point of view and the finding of the psychiatrist can be communicated and informally discussed with the referring physician and other members of the clinic.

There is an important problem in working out some practical and effective forms of therapy, even though they may be purely symptomatic, for the patients who are referred to the psychiatric clinic.

*Laxity of the Radio-ulnar Joint Following Colles Fracture.* R. K. LIPPMANN. Arch. Surg., 35: 772, October 1937.

The mechanism of tear of the dorsal radio-ulnar ligament in association with Colles fracture is explained. Evidence is presented indicating that the lesion accounts for many instances of long standing pain after Colles fracture.

Recognition of the tear immediately after reduction of the fracture is important because at this time conservative treatment is usually successful. Supination of the forearm approximates the torn edges, and maintenance of this position for two to three weeks permits healing. This prevents subsequent radio-ulnar joint laxity.

A simple operation for the repair of old tears of the ligament is described.

*Dynamics and Therapy of Depressive States.* S. LORAND. Psychoanalyt. Rev. 24: 337, October 1937.

Two cases of psychogenic depression and their analyses, lasting over three years in regular five hour a week sessions, are presented, including a general discussion in this connection of the psychological basis and structure of depression. In both cases

the analysis revealed infantile neuroses as the underlying fertile basis for the later illness.

The fundamental distrust from which these patients suffer seems to be due to their early childhood frustrations, especially those inflicted by the mother. Both patients studied had suicidal tendencies, slight delusions, various forms of anxiety, and strong, repressed aggressiveness. In both, the conflict—as is usual in depressive states—centered around the mother, but also involved other members of the family. The frustrations of early childhood had made these patients over-sensitive, because they also implied a threatening and punishing attitude on the part of the mother.

The adjustment in therapy of such patients depends on the ego function. This will also prove the determining criterion for the selection of cases which are amenable to analysis. The plastic and unstable ego may imply extreme regressive tendencies; a stronger, rigid ego may prove capable of restitution.

This paper stresses the point that the psychoanalytic therapy of these patients may have to be modified in many respects from what is usual in analytical treatment.

*Fairy Tales, Lilliputian Dreams, and Neurosis.* S. LORAND. Am. J. Orthopsychiat. 7: 4, October 1937.

This presentation deals with dreams which have a fairy tale content. It is a sequel to an earlier paper dealing with clinical material in which a connection was shown to exist between an adult neurosis and fairy tales told to the patient in childhood, the structure of the whole adult neurosis being based on folklore material. Analytical treatment of persons presenting such dreams gave important clues to the rôle which fairy tales, fantasies, and the experiences of early childhood play in character formation and in the creation and maintenance of neurotic difficulties.

Other circumstances of importance in connection with the telling of fairy tales are discussed: possible harmful or beneficial effects, why they are in one instance the source of pleasure and intellectual stimulation, in another the source of neurotic disturbance, how they may create a permanent attitude in the child's unconscious; and their importance as a means of sublimation of childhood conflicts. Also, how the content and manner of telling the stories in childhood have to do with the states of pleasure or anxiety that accompany them and later recur in dreams. A savage tale, for example, told to intimidate, demands complete surrender of all tender, perhaps sexual, tendencies in childhood. In adult life this surrender may become the problem of a neurosis; whereas a mild, helpful story, or one that is only incidentally or slightly threatening, may present a less acute problem in later life, or none at all.

*Bursitis of Sartorius Bursa; an Undescribed Malady Simulating Chronic Arthritis.* E. MOSCHCOWITZ. J.A.M.A. 109: 1362, October 23, 1937.

This disease is fairly common. For an unknown reason the malady occurs almost exclusively in women. The history is quite characteristic and pathognomonic. These patients complain of pain in both knees on ascending or descending stairs. Walking on the level is not painful in the least. On examination, movement of the knee joint in both extension and flexion causes no pain. The joint itself is not tender. On the other hand, a tender area is found on the inner tibia at the exact site of the insertion of the conjoined tendon of the sartorius, semitendinosus and gracilis tendons. Occasionally a slight swelling is found in this area but, as a rule, only tenderness is present. X-ray examination of the joint reveals no evidence of arthritis. In a few instances lateral x-ray films of this area showed nothing abnormal. In almost every instance the patient had large lower limbs, out of proportion to the size of the body. In some instances there was overweight. According to Quain, there are two bursae in this region: 1, the bursa anserina between the conjoined tendon of the gracilis and semitendinosus muscles and the head of the tibia, and, 2, the bursa mus-



culi sartoria propria lying between the tendon of the gracilis and semitendinosus muscles. Occasionally there is a communication between these two bursae. In all probability the bursitis results from strain in the use of the sartorius and gracilis muscles, which act to lift the body in stepping upward and downward.

The best results are obtained by treatment for reduction of weight. Obviously, the recognition of the disease is important from the point of view of prognosis.

*Fibroblastic Tumors of the Extremities.* E. M. BICK. Arch. Surg. 35: 841, November 1937.

Fibroblastic tumors are among the most common of all tissue tumors involving the extremities; they are exceeded in number only by the benign lipoma. By definition a fibroblastic tumor is a neoplasm of mesodermal origin composed of cells whose ultimate function is the production of fibrous connective tissue. They vary in structure within the limits of precursing tissues and adult connective tissue variations. In the benign form it is known as fibroma; in the malignant form, as fibrosarcoma. Variations in histology, which heretofore have been given distinctive names, such as angiosarcoma or myxosarcoma, offer no differences in their clinical manifestations, response to therapy or prognosis. Therefore, to retain these names merely adds to the confusion.

In the treatment of fibroblastic tumors of the extremities the following rule can be adopted: adequate primary excision when feasible is sufficient for the primary tumor. No cases in which this has been fully accomplished have died without at least one local recurrence. Local recurrence demands amputation, since no case is on record which has survived simple excision of a recurrence. Cases of repeated excision are on record but the disease has not been halted and practically all have died within a five-year period. Radiation under present technique has been entirely futile.

*Acute Anterior Poliomyelitis in New York in 1935. A Review of Six Hundred and Eighty-six Cases.* A. E. FISCHER AND M. STILLERMAN. Am. J. Dis. Child. 54: 984, November 1937.

An analysis of 686 cases during the poliomyelitis outbreak in the city of New York in 1935 was undertaken. The seasonal incidence and the distribution as to the age, sex and color of the patient were recorded. The tendency for the disease to attack older persons was greater than previously. The communicability was low; thirty-six cases occurred in seventeen, or 2.5 per cent of the families. One case of recurrent poliomyelitis was found in this series. The proportion of patients paralyzed was highest in the very young, fifty-one of fifty-three children under two years being paralyzed, and in patients over thirty, six of seven being paralyzed. Paralysis developed in only 20 per cent of the patients that entered the hospital in the preparalytic or meningitic stage. The nonparalytic attacks were probably caused by the poliomyelitis virus, rather than by other viruses that attack the central nervous system. The temperature was the best criterion of the activity of the disease. In eight of twelve cases in which the spinal fluid contained over 500 cells per cubic millimeter, paralysis either was present or developed shortly. In ten cases poliomyelitis occurred within one month after a tonsillectomy and adenoidectomy, and in five of these there were bulbar or encephalitic manifestations. One case of poliomyelitis occurred in a patient who was in her eighth month of pregnancy. A strongly positive reaction to the Schick test was frequently found early in the disease. Treatment in the Drinker respirator of patients with respiratory embarrassment, due to paralysis of the muscles of the chest or diaphragm, was satisfactory. The mortality rate for the 686 cases, 2.6 per cent, was the lowest ever recorded in New York City.

*Bilateral Atrophy of the Optic Nerve in Periarteritis Nodosa. A Microscopic Study.*

I. GOLDSTEIN AND D. WEXLER. Arch. Ophth., 18: 767, November 1937.

Typical lesions of periarteritis nodosa occur in the choroid, for the most part, and, occasionally, in the posterior ciliary and scleral vessels. In the present case, the fundi showed atrophy of both optic nerves and the disappearance of most of the pigment of the choroid. Microscopically, there was severe disease of most of the choroidal arteries, and of the posterior ciliary arteries, including those supplying the nerve head. The rod and cone layer was atrophic. There was inflammatory round cell infiltration of the nerve. The neuritis thus produced was held responsible for the loss of vision, but the disturbance in the neuro-epithelium was undoubtedly a contributing factor.

*Hematological Observations on Bone Marrow Obtained by Sternal Puncture.* P. VOGEL,

L. A. ERF AND N. ROSENTHAL. Am. J. Clin. Path. 7: 436; 498, November 1937.

The purpose of the paper is to evaluate the simple puncture method of Arinkin as a routine diagnostic procedure and to report changes in the marrow during the course of various diseases, especially blood dyscrasias. Two hundred and forty-six cases were studied and the findings in typical examples presented. Certain investigative possibilities are suggested. The authors point out the diagnostic, prognostic and corroborative value of sternal aspiration in certain diseases.

*Nephrectomy versus Conservative Operation in Unilateral Calculous Disease of the Upper Urinary Tract.* G. D. OPPENHEIMER. Surg. Gynec. & Obst. 65: 829, December 1937.

The statistics for the operative treatment of calculous disease of the kidney on Dr. Beer's service for the years 1928 to 1933 are presented. The "true" recurrence rate for conservative operations in the primary stone cases was 8.1 per cent while in the secondary stone cases, it was 28.3 per cent. The prevention of pseudo or "residual" recurrences by operative x-ray control is discussed. Notwithstanding statistical and other considerations suggesting the advantages of primary nephrectomy in certain borderline cases of unilateral calculous disease, the author believes that pyelolithotomy, pyelonephrolithotomy or nephrolithotomy with operative x-ray control are the procedures of choice.

*Excretion of Foreign Substances by the Liver and the Question of Visualization of the Gall Bladder in the Presence of Jaundice.* R. OTTENBERG. Am. J. Roentg. 38: 859, December 1937.

A brief review is given of the factors which determine excretion of foreign chemical substances by the liver, discussing the question whether it is justifiable to attempt gall bladder visualization in the presence of jaundice. It is concluded that if one uses good judgment in selecting cases in which the liver function tests do not indicate grave damage to the liver parenchyma, one is justified in attempting gall bladder visualization in the presence of jaundice.

*Phenomenon of Local Skin Reactivity to Bacterial Filtrates: Its Relation to Anaphylatoxins, Forssman Antibodies and Serum Toxicity.* G. SHWARTZMAN. J. Infect. Dis. 61: 293, November-December 1937.

Studies by the author of this paper and other investigators indicate clearly that, in spite of superficial resemblance, the provocative factors of the phenomenon of local skin reactivity bear no relationship to anaphylatoxins. There are some indications that the complexes of Forssman antigen and antibody may be endowed with provocative potency in the phenomenon.

The provocative potency of whole blood of man and guinea pig may be due to some in vivo interaction between the blood and the natural antibodies of the rabbit.

The purpura-producing serums of Ledingham, Bedson, and Roskam bear no relationship to the phenomenon of local skin reactivity.

*Mono- And Polymolecular Films Of Physiologically Active Substances.* H. SOBOTKA.

Publication of The American Association For The Advancement of Science, pages 54-60. No. 7, December, 1937.

Monomolecular layers may be situated at the boundary in any system consisting of two phases, the various possibilities being briefly discussed. "Mono-layers" on a liquid-gas interface, i.e. monolayers spread on the surface of a liquid, have been successfully studied in recent years. Their properties, on the one hand their analogy to the behavior of three-dimensional aggregates, the common applicability of laws governing intermolecular forces, and on the other hand the special properties due to the dorsiventrally asymmetrical orientation in such films, form the fundament of what one may call "two-dimensional chemistry." The study of mechanical and electrical properties as well as of the chemical reactions with substances dissolved in the liquid phase and of the incidental diffusion and penetration phenomena, harbors numerous preparative and microanalytical possibilities. The application of these principles has been essentially widened by Langmuir and Blodgett's studies of built-up films. The new technique of building films of a known number of monolayers on prepared slides opens new avenues for research in organic and biological chemistry. Reactions of built-up films submerged in fluids and solutions permit the study of interaction in systems like sterols with saponins, bile acids with lipids, enzymes with their substrates, and antigens with their antibodies. In collaboration with E. Bloch, the author has studied monolayers of various hemoglobin and chlorophyll derivatives, copro- and uroporphyrins the peculiarities of which are discussed. Many systems of biological importance include proteins. These may, in some instances, be built up from monolayers spread on water or otherwise by adsorption from solution on heavy-metal conditioned slides, or, finally, by specific adsorption on slides with specific reaction partners. The knowledge gained from these experiments—by optical methods for the estimation of thickness, of contact angles, of diffusion and penetration, skeletonization and other typical operations—as to molecular dimensions, angles of orientation, structural features, other physical properties and chemical reactivity—can be interestingly correlated with facts established by x-ray spectroscopy, electron diffraction, ultracentrifugation, etc. A new tool has been won for the elucidation of structure and reactivity of many classes of substances, especially in the field of immunology, enzymology and in the structural investigation of proteins and other megamolecules.

*Emptying of the Normal Gallbladder.* M. L. SUSSMAN. Am. J. Roentg. 38: 867, December 1937.

The normal gallbladder in fasting individuals or in those on a carbohydrate diet does not contract for at least five days and probably stays filled much longer. The tetraiodophenolphthalein is absorbed by the gallbladder mucosa.

Gallbladder evacuation depends on the production of cholecystokinin, which, in turn, depends upon the introduction of fats or acids into the duodenum in fairly high concentration.

The normal gallbladder usually empties to less than half its size within thirty minutes after the administration of three egg yolks, and the cystic duct, and also often the common duct, can be demonstrated. This provides a valuable confirmation of normal function.

Function cannot be considered abnormal when there is delayed emptying. A second egg yolk meal should be given. Pylorospasm or pyloric obstruction must be excluded as possible causes.

The biliary ducts often remain visualized for fifteen to twenty minutes due to the primary action of cholecystokinin, namely, contraction of the gallbladder and increased intramural resistance at the sphincter of Oddi.

Morphine completely prevents evacuation of the normal gallbladder after a fat meal. This is apparently due to spasm of the sphincter of Oddi and not to a relaxation of the gallbladder musculature: pylorospasm is also an indirect factor. Visualization of the biliary ducts is therefore not obtained. Nitroglycerin also produces a definite but temporary inhibition of gallbladder emptying.



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Manuscripts, abstracts of articles, and correspondence relating to the editorial management should be sent to Dr. Joseph H. Globus, Editor of the Journal of The Mount Sinai Hospital, 1 East 100th Street, New York City.

Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

## THE WILLIAM HENRY WELCH LECTURES

## I. NEW LIGHT ON THE BIOLOGICAL RÔLE OF VITAMIN E

HERBERT M. EVANS

*(Director of the Institute of Experimental Biology, University of California)*

Over a decade ago, at the conclusion of our long program of studies on the rôle of vitamin E in the physiology of reproduction in higher animals, Burr and I (1) permitted E-low mother rats to attempt to suckle and, if possible, rear their young. Although they had been given but little more vitamin E than had proved necessary to insure the birth of living young, if vitamin B was high lactation was not seriously interfered with and the young grew normally and, to all appearances, thrived. Suddenly, towards the end of the lactation period, a calamity intervened for we were surprised to find that the majority of these well-nourished young developed a mysterious malady, characterized mainly by muscular paralyses. Half of the affected sucklings died from the malady—often so suddenly that there were no signs of wasting from undernutrition. The disorder was not due to constitutional inferiority of the young through germinal impairment or any inadequacy in their intrauterine life because, though diminished, the disease also occurred when we allowed young from normal, natural food mothers to suckle from these E-low mothers. The disease was therefore unquestionably due to defect in the E-low mother's milk, and the final proof of this was secured by shifting her and her own litter to natural foods, in which cases the paralysis never occurred. We then began the addition of single nutritive elements to the diet of other E-low mothers; these efforts were without effect until vitamin E was given them—in the least contaminated form then available, wheat germ oil or concentrates from its non-saponifiable fraction. To put the cap on the proof, the direct administration of these substances to the young was similarly completely effective in preventing the disease. This previously unknown need for vitamin E in the economy of the developing young was remarkably limited in time; the paralyses were prevented if the substance was given as late as the fifteenth day of life; the disease otherwise developed by the twenty-fifth day of life—so that this ten-day period is a critical one as regards need for vitamin E.

While we were absorbed in other studies, primarily those concerning the

<sup>1</sup> Delivered at The Blumenthal Auditorium, The Mount Sinai Hospital, New York City, October 20, 1939.

nature of vitamin E itself, Olcott (2) examined the muscular system in these young and discovered a remarkable widespread degeneration quite exactly resembling that reported by Goettsch (3) and by Goettsch and Pappenheimer (4) almost ten years ago in their E-low guinea pigs and rabbits, to which I shall revert presently. Lipshutz (5) had reported definite cerebrospinal lesions in these young but had neglected a simple examination of the musculature. Olcott's finding was spectacular. It showed that the Goettsch-Pappenheimer discoveries could be extended to other mammals and, above all, to the form in which the paralysis had been first noted. Now it is highly important to note that in all our work it has been demonstrated that a certain number of young never develop the paralyzes, a certain number completely recover, spontaneously, without any form of treatment, and a certain number recover with permanent paralyzes. In our 1928 paper we reported that the last-mentioned animals, except for the paralyzes, may exhibit every evidence of normality and health. We reared large numbers of them and retained them for a significant part of their life span. Many were bred and when vitamin E was administered early in gestation and in lactation, the young were normal in every way. These older animals then suffered grave localized disability but only this, and, as Ringsted (6) has emphasized, they never die from this cause but from some intercurrent infection. Ringsted was the first to recognize that animals which escape the early paralysis because they are taken from natural food mothers and are placed on the E-free diet only after weaning, nevertheless after some months gradually develop well localized disabilities—paralyzes. These were then reported by Burr, Brown and Moseley (7), by Knowlton and Hines (8, 9) and by us (10). Finally Einarson and Ringsted (11) have given us a careful exploration of the spinal cord, as well as muscles, of these older animals and have described stages in the cord lesions which begin with the dorsal roots and the proprioceptive tracts of the fasciculi cuneatus and gracilis, then involve the anterior horn cells and ventral roots, and finally, in some cases, the pyramidal tracts. They state that the cord lesions therefore "resemble closely a combination of two of the most important systemic degenerations occurring in man—namely tabes dorsalis and spinal progressive muscular atrophy." As to the muscles, their opinion is that the lesions remind one of a muscular atrophy of spinal origin, i.e., a neurogenous muscular atrophy, especially the marked proliferation of the marginal nuclei and the absence of hypertrophic fibers, though they admit that in the early stages resemblances to a pure myogenous atrophy are found. They emphasize the possibility that injury to the autonomic innervation of the musculature is primary, and that a secondary involvement of the cerebrospinal system occurs, giving at first the picture of tabes and then of amyotrophic lateral sclerosis.

The cause of the death of E-low paralyzed sucklings is at present a



mystery but it could conceivably be ascribed to paralysis of the muscles of respiration. An elaborate electrocardiographic study has not shown us cardiac impairment and the myocardium is histologically normal. I have already mentioned the occasional, spontaneous and complete recovery of young sucklings so badly paralyzed that they could not right themselves when placed on their backs. Some of these spontaneous recoveries have been sacrificed when forty-five days of age and their striated musculature is histologically normal and normal in creatine content, whereas this is never the case at the time of paralysis.

Barrie (12) of England in 1938 demonstrated that alpha-tocopherol prevents the paralysis and death of these suckling young, followed promptly by a similar demonstration independently undertaken by Goettsch and Ritzmann (13) of New York. We, in Berkeley, had under way a similar long series of experiments and have had no trouble in verifying these results. Goettsch and Ritzmann gave a total of 5 milligrams of alpha-tocopherol to each suckling young between the tenth and twenty-fifth day of life. We have given one milligram daily in the same interval and have found it protective. But it is easier and just as reliable to treat the young by way of the mother so that her milk contains the substance, for the disease is invariably prevented when the mother is given a single dose of 6 milligrams of alpha-tocopherol on the day of littering.

Now, as previously mentioned, as a matter of fact, the lesions of the striated musculature were not first produced in rats, but in rabbits and guinea pigs deprived of vitamin E, and we can now say that when care is taken to insure that adequate amounts of the vitamin B complex are coincidentally present, alpha-tocopherol acts in the case of these animal forms also to cure or prevent paralysis and death. (Mackenzie and McCollum (14) 1939; Shimotori (15) 1939.)

It is to Goettsch and Pappenheimer, who were interested in the production of vitamin E deficiency in a species other than the rat, that we must ascribe the discovery that rabbits and guinea pigs reared on a diet in which the vitamin E had been destroyed by treatment with ferric chloride, develop a deficiency disease characterized by dystrophy of the voluntary muscles. In their earliest experiments it was unfortunate that the addition of wheat germ oil to the diet appeared only to delay the onset of the dystrophy but not prevent it, although Mattill (16) subsequently found that the inclusion of 2 per cent wheat germ oil was at least adequate to prevent the development of dystrophy in rabbits for many months, during which time the animals grew normally, and Mackenzie and McCollum (14) have lately shown the effectiveness of alpha-tocopherol if B is high.

Morgulis and co-workers (17, 18) felt that at least two factors, both present in whole wheat germ, were required for the prevention or cure of the disease in rabbits. One factor was soluble in 70 per cent ethanol and the other in typical fat solvents. The latter factor was present in the

unsaponifiable fraction of wheat germ oil and was, in all probability, vitamin E. The most recent development here seems decisive, for it was with the Goettsch and Pappenheimer diet, supplemented with 10 per cent ether-extracted wheat germ, that Mackenzie and McCollum, employing rabbits, have been able to note the curative effect of alpha-tocopherol in connection with this experimental muscular dystrophy. A decrease in muscle creatine is invariable in dystrophic animals and there is always a corresponding increase in urinary creatine. This led Mackenzie and McCollum to devise an ingenious method for predicting the onset of the dystrophy. Vitamin E therapy in this way could be initiated a few hours before obvious paralysis would otherwise appear.

Madsen, McCay, and Maynard (19, 20) at Ithaca have for some years been interested in devising purified diets for guinea pigs and rabbits; in the course of these studies they found when cod liver oil was included in the ration that these animals succumbed from a muscular dystrophy. When the unsaponified fraction of cod liver oil was given in place of the oil itself the dystrophy was not prevented, although its onset was delayed. Likewise the omission of cod liver oil and the use of irradiated yeast and carotene as sources of vitamins A and D did not prevent the eventual development of muscular lesions, although the onset was delayed. Madsen, McCay and Maynard believed that cod liver oil, particularly its saponifiable fraction, contained some toxic factor hastening the degeneration of the skeletal musculature but that a second factor must be admitted to be involved in the trouble. The complicity of cod liver oil in their results was at first confusing, for we knew from the studies of Agduhr and Stenström (21) that this substance is toxic in many ways—for instance to the cardiac musculature. Moreover, to make matters worse, the Cornell investigators were able to show that the addition of cod liver oil or concentrates to a natural food diet resulted in muscular dystrophies. Mattill (22, 23) has made the ingenious suggestion that in herbivores which have a large cecum, food could remain long enough for autoxidative changes to progress farther and more rapidly than in omnivorous animals such as rats. "From this point of view," he said, "the long search for a toxic factor in cod liver oil and for cures of the disorders produced thereby may have been following a wrong trail." That it is not merely to the anti-oxidative properties of a curative substance that we must ascribe effects was also shown by Mattill when he reared rabbits on a synthetic diet devoid of E but with an anti-oxidant; they developed the dystrophy and succumbed in the usual way. Finally, even using cod liver oil, Miss Shimotori in our laboratory has been able to prevent the dystrophy by administering alpha-tocopherol to guinea pigs reared on the Madsen, McCay and Maynard diet, the alpha-tocopherol and cod liver oil being administered on alternate days.

It is highly interesting that characteristic disturbances and death occur in birds when the attempt is made to rear them without vitamin E. We

owe our knowledge of these conditions almost exclusively to the Pappenheimer and Goettsch group. They have shown that chicks deprived of E develop a nervous disorder, called by them encephalomalacia, goslings a degeneration of the skeletal musculature, and turkeys an ideopathic degeneration of the smooth musculature of the gizzard. Here again delay in ascribing the disorders solely to the lack of E was occasioned by the annoying finding that they were not prevented by the addition of certain natural foods known to contain E—grain products including wheat germ and greens. Furthermore, when natural foods were treated with  $\text{FeCl}_3$ , although vitamin E was effectively destroyed, the paralysis disease was prevented, but Dam of Copenhagen (24) and Pappenheimer, Goettsch and Jungherr (25) have here also in the last few months shown that alpha-tocopherol will prevent chick encephalomalacia.

No more remarkable example of species specificity in reactions to vitamin need could be furnished than that found in the Columbia studies on domestic birds, for the gosling has the muscular paralyses of young mammals and dies just as suddenly and mysteriously, while in the chick disorder we have an equally good example of pure involvement of the nervous system—albeit a secondary involvement, for the Columbia studies showed clearly that involvement of the chick's nervous system was secondary to a peculiar impermeability of the blood vessels supplying the nervous tissue. "We have not been able," they say, "to bring proof that the capillary thrombosis is a primary cause of the ensuing necrosis. Indeed, it may well follow upon a prolonged vaso-constriction or vasomotor paralysis or the first followed by the second." May not, therefore, a primary injury to the sympathetic nervous system be involved here, as Einarson (11) supposes to be the case in the myopathy of adult rats where cerebrospinal lesions are absent. We could thus harmonize the two astonishingly different pictures produced by lack of the same substance E, the massive necrosis of cerebellar tissue in the chick, and the muscle fibers in duck and mammal.

I think we may regard it as settled that a characteristic muscular atrophy and obscure fatality occur in divergent mammalian forms when vitamin E is withdrawn and that normality is assured with the same diets, providing the pure substance alpha-tocopherol is administered prophylactically. There are probably manifold slighter deficiencies of the body when inadequate amounts of the vitamin are given but when the amounts are nevertheless sufficient to prevent muscular atrophy. A good example is furnished by the decline in the growth of E-low rats after the fourth month of life—a condition promptly relieved by the administration of vitamin E.

With the isolation of alpha- and beta-tocopherol and the synthetic production of these two pure substances our concept of their chemical nature is complete. They are the chromane substances represented by the formulae on the following page.

John of Goettingen (26) and we, independently at Berkeley, in con-



junction with L. I. Smith of Minnesota (27, 28), have found a certain degree of vitamin E activity in an astonishing range of substances. Von Werder et al. (29) in Germany and Todd and his associates (30) in England have also extended the list and range of these substances. If, in fact, one feeds very high levels of the aromatic nucleus of tocopherol, in the form of tetramethyl hydroquinone, the fertility of sterile females can be reinvoled with single doses of 100 milligrams. This high melting and relatively insoluble substance is probably poorly absorbed, otherwise it might be even more effective than we have found it to be. Karrer (31) has shown that the presence of the methyl groups in the benzene ring plays a very important rôle because the dimethyl tocopherols, beta- and gamma-, are distinctly less active than alpha-tocopherol; Karrer synthesized the mono-methyl tocopherols and found them inactive. The nature of the aliphatic

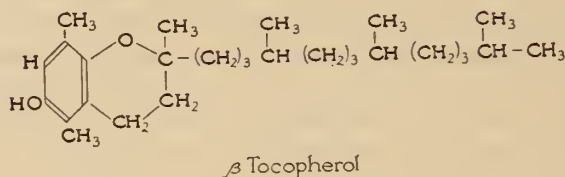
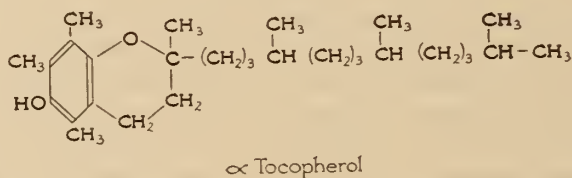


FIG. 1

part of the tocopherol molecule is also important, but here it is very hard to make any simple generalization of the relation of structure to vitamin activity, since, as already mentioned, duro-hydroquinone which has no long side chain whatever, nevertheless shows considerable activity, and many substances having side chains which approximate that of the tocopherols have no activity. It is hardly necessary to remind you of the analogous situation furnished by vitamin D. Calciferol, in the rat at least, possesses enormous vitamin D activity; yet the replacement of a hydrogen by a methyl group in the side chain gives a compound which Windaus found completely inactive. On the other hand, the vitamin D<sub>3</sub>, which is a natural substance occurring in fish liver oils and can be produced by irradiating dehydrocholesterol is extremely active, although its side chain differs in several respects from that of calciferol. Bills and Hickman (32-35) have brought forth evidence to show that there is a potent vitamin D in



fish liver oils with a very much shorter side chain than any of the before-mentioned compounds.

Alpha-tocopherol can be oxidized to varying degrees by various procedures. The mildest oxidation, that accomplished by controlled action of  $\text{FeCl}_3$ , opens the ring giving the para-quinone (alpha-tocoquinone), as shown by John (36, 37). We have found that tocoquinone is active in the cure of sterility at 3 mg.<sup>2</sup> (figure 2).

A somewhat more drastic oxidizing agent—dilute nitric acid in alcohol—oxidizes tocopherol and all 6-hydroxy chromanes in an unusual and interesting manner which has been recently cleared up by Smith, Irwin and

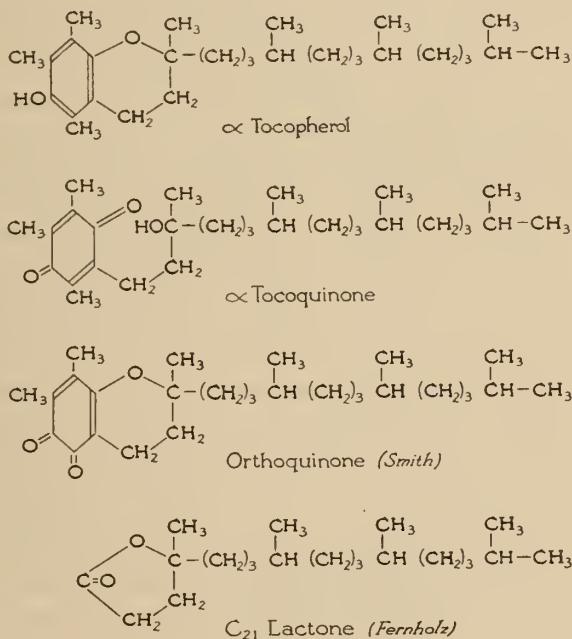


FIG. 2

Ungnade (38, 39). A methyl group is eliminated with the formation of an orthoquinone. The reaction with alpha-tocopherol gives a red orthoquinone which forms a phenazine with orthophenylene diamine, but neither quinone nor phenazine crystallizes. More drastic oxidation with permanganate or chromic acid shatters the aromatic ring giving a lactone which includes merely the aliphatic part of the molecule.

Windaus (40) has stated that the biological rôle of vitamin E might conceivably be explained by its action as an oxidizing-reducing system, of which a number of analogous examples exist among biologically important substances such as ascorbic acid and glutathione. He pictured the toco-

<sup>2</sup> J. Biol. Chem. (in press).

pherol being oxidized to the quinone and then reduced back to the tocopherol. Whether this concept is true or not remains for future work to show. Several investigators have shown that the quinone can readily be reduced to a hydroquinone which can lose water to give tocopherol itself. This loss of water can be effected very rapidly by the catalytic action of strong acids but this is unfortunately not a physiological condition. Without the presence of acids the hydroquinone can be distilled in high vacuum unchanged. According to our experiences the tocoquinone is about as active as alpha-tocopherol.

Now is perhaps the time to poise the basic question of whether or not that particular part of the molecule of alpha-tocopherol responsible for the cure of female sterility is the same chemical configuration responsible for the prevention or cure of the pathological conditions in the nervous and muscular systems already described. Waddell and Steenbock (41) some years ago introduced an ingenious method for the destruction of vitamin E in natural foods. An ethereal solution of ferric chloride was sprayed upon and thoroughly mixed with the food, sterility resulting in male rats from such a diet. The action of  $\text{FeCl}_3$  in the destruction of E has been interpreted as a catalytic hastening of atmospheric oxidation. It is in fact possible in this way to decrease or destroy vitamin E in the highest known natural source of it, that is, in wheat germ, for the oil subsequently extracted from such germ does not invoke fertility at 20 gram doses, whereas otherwise a gram is invariably efficacious. Such wheat germ oil, thus enormously reduced in its fertility-conferring power, is nevertheless effective in the prevention of the muscular dystrophy of suckling young rats when fed from the tenth day on. (Goettsch and Ritzmann (13).) We had a somewhat parallel experience in the restoration of normal growth to E-low females characteristically slowed at the fifth month. We had permitted ferric chloride to act on wheat germ oil and had destroyed at least nine-tenths of its fertility-conferring power, but not its power to promote growth. The above experiments bring up the question of whether the same chemical configuration in alpha-tocopherol is needed for the normality of both growing embryos and the post-natal development of the muscular and nervous systems, very considerably lower levels sufficing for the last-mentioned requirements, or whether while tocopherol will invariably prevent neuro-muscular abnormality, portions of the tocopherol molecule which are not curative of sterility will do so equally well.

A settlement of this question has not yet been effected but may be reached by comparing the kinds of biological efficacy unfolded by various oxidative degradation products of tocopherol. The paraquinone still retains most of its fertility-conferring power, although it may be emphasized that its absorption spectrum in the ultraviolet differs considerably from that of alpha-tocopherol typical for the unaltered tocopherol molecule.

We are now in process of testing the lactone.

As will also be the case in the second lecture of this series, you will observe perhaps with disappointment that unsolved rather than solved problems have been brought to the fore. The latter have not been neglected—the triumphs of research in this field have been emphasized wherever they have been secured but the delineation of known and unknown, as light and darkness, gives desirably sharp boundaries to our knowledge and is preferable to envisioning a field as all twilight or the light before dawn. I have not felt it necessary to take the time to deprecate premature claims for the widespread need of vitamin E on the part of domestic

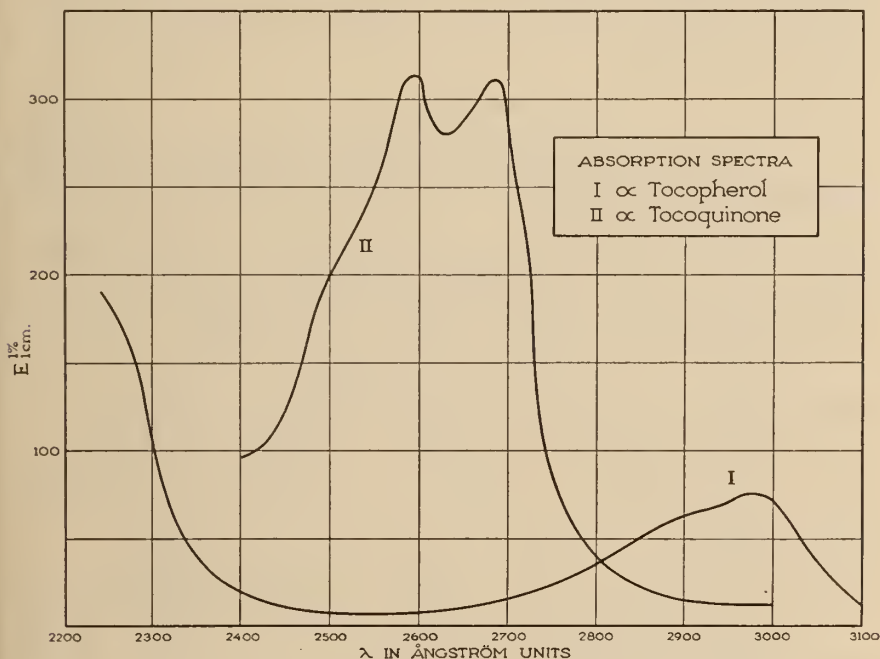


FIG. 3

animals or human beings, though this may well turn out to be the case. The myopathies in man will soon be investigated empirically with toco-pherol but it is necessary to emphasize that this has been shown to be primarily, if not entirely, a prophylactic, rather than a curative, agent. Beginning deficiencies and especially those of purely myogenous origin may conceivably be helped by it, but this domain constitutes territory which I have characterized as not yet with light. Nothing would be more welcome could it occur, for it has been well said that medical practice has remained "awestruck and bewildered in the presence of diseases ravaging the muscles, the physician only too often being no more than a helpless onlooker watching the progressive course of deterioration."

I would return to characterize the outstanding enigmas in the field I have sought to bring before you—enigmas which I do not doubt may be resolved by physicians and investigators in this audience. They are:

1. What is the "specificity" of chemical structure in vitamin E responses and are different chemical portions of the tocopherol molecule necessary for reproductive and neuromuscular normality?

2. What is the actual mode of action of the vitamin in the physiology of embryos, seminiferous epithelium and neuromuscular apparatus?

3. What is the cause of the death of E-free sucklings and how does spontaneous recovery ensue?

4. What analogous human clinical conditions exist either of myogenic or neurogenic origin?

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## PALLIATIVE PARTIAL GASTRECTOMY FOR CARDIAC GASTRIC ULCERS

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*(From the Second Surgical Service)*

While the operation of either partial or subtotal gastrectomy may still be a controversial point in the surgical treatment of duodenal ulcers, its adoption has been accepted almost universally in cases of gastric ulcer. However, the mortality of subtotal gastrectomy in gastric ulcers would be definitely increased if a routine attempt were made to radically remove those high ulcers situated either on the lesser curvature of the cardia near the esophagus, or on the posterior wall of the stomach penetrating into the body and tail of the pancreas. For, in order to extirpate some of the chronic calloused ulcers in these particular areas, a complete gastrectomy would be necessary. The mortality in total gastrectomy is at present almost prohibitive because of the great technical difficulties involved. On the other hand, if a gastrectomy were to be dispensed with, even the local excision of a callous ulcer in the vicinity of the cardia, supplemented by a posterior gastro-enterostomy, would involve enormous hazards because of the extensive inflammatory infiltration present. Gastro-enterostomy alone for cardiac ulcer has not been a very satisfactory procedure in our hands, although the gastric acidity may have been lowered somewhat by duodenal regurgitation.

It has been shown both experimentally and clinically that the removal of the antrum in a partial gastrectomy tends to produce a gastric anacidity, especially in cases of gastric ulcer. Recurrence of ulceration in the presence of an anacidity is most rare; in fact, it is almost unheard of. Therefore, ulcerations situated high in the cardiac portion of the stomach would be indirectly benefited by a partial gastrectomy, for with the removal of the pyloric and antral areas of the stomach, the resultant anacidity should be favorable to the spontaneous healing of any ulcer in the remainder of the stomach.

Madelener (3), in 1923, performed a pylorectomy with a Billroth I anastomosis without removal of the ulcer in a patient with an hour glass deformity of the stomach due to a gastric lesion penetrating into the middle of the pancreas. He subsequently performed the same procedure in two cases in which, in order to effectively remove a callous ulcer situated high in the lesser curvature, a total gastrectomy would have been necessary. These cases made an uneventful recovery, and when seen subsequently were free of their symptoms. Although a condition of anacidity was

only produced in the first case, test meals showed a marked diminution of free and total acidity in the other two. X-ray examination disclosed the disappearance of the gastric ulcer in all patients. Surgeons have come to realize that simple pylorotomy is not a good operation in the treatment of gastroduodenal ulceration. If the operation is to be really effective, the antrum too must be removed. Flörcken (2), in 1923, performed a partial gastrectomy without removing the ulcer which was situated high on the lesser curvature. He suggested that this procedure be called "palliative gastric resection."

Wells (5), in 1933, evidently unaware that Madelener and Flörcken had previously employed this operation, suggested a palliative gastrectomy for high gastric ulcers. He reported four cases of chronic gastric ulcer in which a Polya-Moynihan partial gastrectomy was performed, the line of resection being made distal to the ulcer. Walker (4) recently reviewed the original four cases of Wells and added six more, making a total of ten. He stated that surgery was advised in these cases only when medical treatment had failed, and in two cases because there was a suspicion of malignancy. In all these patients, the ulcer was located high on the lesser curvature, either adherent to the liver or pancreas or both. The operators felt that under the pathologic conditions, posterior gastro-enterostomy would be of little avail and that gastrectomy would be very difficult and attended with a considerable risk. A palliative gastrectomy was therefore performed under general anesthesia, supplemented by novocaine infiltration of the splanchnic plexus. The type of anastomosis was the ante-colic Polya-Moynihan, except in one case in which, because of the fixation of the ulcer to the liver, a retrocolic anastomosis was made. There were no deaths and no serious complications in this series. The subsequent course of the ten cases in which palliative resection was performed was interesting. Nine patients were traced. One received no benefit, but the remaining eight were quite well and at work. Seven cases were recently examined, and in six roentgenograms were made. In this group there were no recurrences.

Recently Didier and Bompert (1) in order to circumvent the difficulties of a radical resection in high lying cardiac lesions, presented a new two stage procedure. A preliminary gastro-enterostomy with a spur is first made and this is followed ultimately by a radical gastric resection. The technique they employ in the operation is as follows: An elliptic gastric resection is made, the base being the greater curvature and the apex, 1-2 cm. below the lesser curvature for the canal between the two pouches, must naturally be as small as possible. The right portion is closed immediately and an anastomosis is established between the left gastric segment and a jejunal loop. The stoma is identical in all points with that in Finsterer's gastrectomy. The stomach now consists of two pouches, the upper one being drained by the anastomosis. At the second operation, the duodenum is divided and closed, the stomach is mobilized from right to left and



resected proximal to the lesion as far as the anastomosis. The operation has the advantage of preserving the lesser curvature eliminating the need for hemostasis in that region, especially when the lesion is accompanied by much infiltration and edema. In one case, at the second stage, three and a half months after the performance of a gastro-enterostomy with a spur, the infiltration about a high lying gastric lesion had become so reduced that a high resection of the stomach was possible.

This two-stage procedure advocated by Didier and Bompert seems to offer no advantages to the palliative gastric resection which can easily be performed in one stage. It must be remembered that this procedure is only indicated in cases in which in order to remove the ulcer radically a total gastrectomy would be necessary.

#### CASE REPORTS

*Case 1. History* (Adm. 416481). H. A., a male 55 years of age, was admitted to The Mount Sinai Hospital on November 10, 1937, and discharged December 9, 1937. His history dated back for one year, about which time he developed the characteristic symptoms of a gastric ulcer. Inasmuch as ambulatory medical treatment failed to relieve his pain, he was admitted to the hospital and placed upon a Sippy diet and a milk drip. His symptoms were temporarily relieved for about three weeks. However he soon returned because of a recrudescence of his symptoms and was readmitted.

*Examination.* The patient was an emaciated, middle aged male. The right eye had been enucleated. There were findings of a chronic bronchitis and emphysema. There was a systolic murmur at the cardiac apex, and the heart was slightly enlarged. The blood pressure was 160 systolic and 90 diastolic. There was obvious sclerosis and tortuosity of the peripheral vessels. There was moderate tenderness in the epigastrium. The liver was palpable 2 cm. below the costal margin.

*Laboratory Data.* The hemoglobin was 98 per cent. A preoperative Rehfuess test meal revealed free acidity, 62° and total acidity, 74° (histamine,  $\frac{1}{2}$  cc. given). X-ray examination revealed a penetrating ulcer of the lesser curvature of the stomach quite proximal to the reentrant angle.

*Operation.* (November 13, 1937; under avertin and ethylene.) The stomach was normal in size but in the cardiac area, in the region of the lesser curvature extending posteriorly, there was a hard indurated mass which invaded and seemed attached to the tail of the pancreas.

A subtotal gastrectomy of the Hofmeister type with a posterior retrocolic gastro-enterostomy was performed without removal of the ulcer. The pathologist reported that 14 cm. of the lesser curvature and 16 cm. of the greater curvature had been removed, and that a chronic gastritis was present.

*Course.* The postoperative course was complicated by a bilateral basal bronchopneumonia. Subsequently the patient was seen repeatedly, and when examined on October 18, 1938 showed a gain of thirty pounds in weight and registered no gastric complaints. X-ray and gastroscopic examinations failed to reveal the presence of the ulcer. Test meal showed an anacidity.

*Case 2. History* (Adm. 415349). J. S., a male, 50 years of age, was admitted to The Mount Sinai Hospital on October 18, 1937, and discharged December 13, 1937. He gave a history of loss of weight, anorexia and epigastric pain for a period of six months. This pain radiated along the sides of the thoracic cage and posteriorly to the left costovertebral area. For two weeks before admission he had noticed tarry stools, and during the five days before admission he had vomited once every day.

*Examination.* The patient was a thin male with a few crepitant râles at both pulmonary bases. The heart was normal. Blood pressure was 142 systolic and 90 diastolic.

*Laboratory Data.* Hemoglobin, 90 per cent; white blood count 11,500, with normal differential. Gastro-intestinal series revealed a large perforated lesion on the posterior wall of the stomach near the lesser curvature. The duodenal bulb showed a persistent deformity on the greater curvature which was thought to be the result of a cicatrized ulcer. Gastroscopy revealed a sharply outlined ulcer which appeared benign. Test meal showed total acidity of 40° and free acidity of 20°.

*Course.* Despite medical treatment, the patient continued to have pain for a period of two weeks. Operation was therefore performed on November 19, 1937, under avertin and ethylene anesthesia. The stomach was found to be normal in size. Above the reentrant angle there was a definite ulcer which was confined mainly to the posterior wall of the cardia, seemingly infiltrating the body of the pancreas. The duodenum appeared normal.

A partial gastrectomy of the Hofmeister type with a posterior retrocolic gastroenterostomy was performed without removing the cardiac ulcer.

The pathologist reported that 11 cm. of the lesser curvature and 17 cm. of the greater curvature of the stomach had been removed and that examination revealed chronic gastritis.

The postoperative course was uneventful aside from a partial dehiscence of the wound on the tenth day. The patient was seen repeatedly after operation and when examined on October 18, 1938, looked well, had gained about ten pounds in weight and was free of epigastric pain. X-ray and gastroscopic examination failed to reveal the presence of an ulcer previously noted. Test meal showed an anacidity.

#### COMMENT

The two cases which are herewith presented were suffering from cardiac ulcers situated high on the lesser curvature of the stomach. Both patients had been treated medically without lasting effect. The severity of their symptoms and the progressive loss of weight demanded surgical intervention. Although both patients were considered poor operative risks, it was felt that because of the location of the ulcer, a palliative gastrectomy would give the greatest chance of relief with the minimal amount of danger.

A subtotal gastrectomy was easily performed without removal of the cardiac ulcer, 14 cm. of the lesser curvature and 16 cm. of the greater curvature being removed in *Case 1*, and 11 cm. of the lesser curvature and 17 cm. of the greater curvature being extirpated in *Case 2*. The postoperative course in both cases was not particularly stormy. They were followed for over a year and checked by gastroscopy and X-ray examinations which failed to reveal the presence of an ulcer. Test meals showed an anacidity. Clinically they were both well.

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## ACUTE YELLOW ATROPHY OF THE LIVER FOLLOWING SULFANILAMIDE THERAPY AND AVERTIN NARCOSIS<sup>1</sup>

REUBEN OTTENBERG, M.D.

A patient died recently of acute yellow atrophy of the liver. There was no autopsy but the clinical course was so typical that there was no doubt about the diagnosis.

### CASE REPORT

*Clinical Course* (Adm. 437902). In the beginning of January a man of 26 developed the gripe; a left otitis media progressed into a mastoiditis. Between January 21 and February 1 he was treated with sulfanilamide, receiving a total of something over 500 grains (about 33 gm.). Following this he developed a severe anemia but without hemoglobinuria or obvious jaundice. The leukocyte picture was not affected. On January 30 his hemoglobin had dropped to 56 per cent and the red cell count fell to 3,000,000. On January 31 a citrate transfusion of 500 cc. was given; a week later the hemoglobin was found to be 76 per cent and the red cell count was 4,300,000. The mastoiditis continued; the fever was not high. On February 21 a mastoidectomy was done following three days of sulfanilamide therapy. The operative anesthesia was begun with avertin (tribromethanol) by rectum.

About ten days after the operation the patient was given a series of general ultraviolet light treatments and was reported to have become "as red as a boiled lobster."

About two weeks after the operation clinical jaundice was noticed. From the start there was nausea but no pain or vomiting and the temperature continued febrile (100°-101°F.). The physician who examined him at the onset of jaundice found the liver greatly enlarged, about four fingers below the free border of the ribs, and slightly tender.

I saw the patient for the first time on March 23 after he had been jaundiced about ten days. At that time he was very weak, showed considerable loss of weight and was markedly jaundiced. The firm, smooth, tender liver edge was easily felt three fingers below the free border of the ribs; the spleen was not felt. The operative wound was healing well. A blood count was essentially normal; hemoglobin 94 per cent; a tourniquet test was positive, indicating already a slight hemorrhagic tendency. The stool was brownish yellow and gave a slight, but unmistakable reaction for the presence of urobilin.

The patient was hospitalized. He did not at first give the impression of being very seriously sick but the jaundice became progressively deeper. The icterus index at the beginning was 36; a week later it was 50, and two weeks later it had reached 60. (This icterus index was done by the acetone precipitate method, which gives values of only about one-third the original Meulengracht method, so that this represents an extreme degree of icterus.) Urobilin persisted in the stools: at times indeed the stools had almost a normal color. Urobilinogen was likewise found in the urine

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<sup>1</sup> Read before the Clinical Society of the Cornell Out-Patient Department, April 28, 1939.



throughout the course of the illness. On one occasion it was found in as high a dilution as 1 to 40.

The blood cholesterol was very low when I first saw the patient, 130 mg. per 100 cc., and the cholesterol esters were reduced to 55 mg. per 100 cc. A week later the cholesterol had sunk to 115 mg. per 100 cc. and the cholesterol esters to 25 mg. per 100 cc. This progressive decline of the cholesterol and cholesterol esters (called "cholesterol collapse" by Thannhauser (1) who first observed it) is of considerable diagnostic and, when combined with a steadily climbing blood bilirubin, of grave prognostic importance. The urine was examined carefully by the Lichtman-Sobotka method for tyrosin, once early and once late during the disease—both times with negative results.

The patient's general condition remained fairly good for about three weeks. On April 10 he began to complain of digestive disturbances, an intense sense of burning in the epigastrium and esophagus, of distension, and abdominal cramps. The abdomen was found distended and there was a suspicion of ascites. There was marked tenderness in both iliac fossae and even rebound tenderness, but no rigidity and no fever. The blood count was normal.

On April 14 the patient began to vomit and the vomitus showed complete absence of hydrochloric acid. The vomiting continued at irregular intervals. After a few days a small amount of blood appeared in the vomitus and the abdominal pain and vomiting became more pronounced, although the temperature remained normal. On April 14 definite ascites with edema of the legs appeared, and from this time on gradually increased. After the first few days of hospitalization the liver definitely diminished in size so that it could no longer be palpated at all. During the last two weeks of his life the patient showed many manifestations of an hemorrhagic tendency—bleeding from the operated ear, minute hemorrhagic papules on the face and neck, positive tourniquet test, and a prolonged prothrombin time by Dr. Quick's method. His coagulation time, however, was normal. The fibrinogen of the blood was greatly diminished (Dr. N. Rosenthal).

The blood urea nitrogen on April 7, at a time when the patient was beginning to develop toxic symptoms, was low, 8 mg. per 100 cc. and the fasting blood sugar was low normal, 85 mg. per 100 cc. The total blood proteins when the first evidence of anasarca appeared were only moderately low, 4.8 per cent, with albumin 3 per cent and globulin 1.8 per cent.

Four days before death the patient gradually passed into coma which, with short interruptions, became progressively deeper.

*Treatment.* On admission the patient was put on a bland diet and the attempt was made to give him as much as 400 grams of carbohydrate, 60 grams of protein and 10 to 20 grams of fat a day. This was supplemented by daily intravenous injections of 10 per cent glucose in normal saline solution, the amount varying from 500 to 2000 cc. every 24 hours. The patient was also given 12 grams of powdered gelatin a day, (the amino acetic acid provided in large amounts by gelatin supposedly helps the liver in detoxification). Meat was avoided in the diet (the experimental work of Mann (2) has shown that meat is very toxic to dogs with damaged livers). Effort was made to administer various vitamins; vitamin B was added to the intravenous infusion and vitamin K, the new anti-hemorrhagic vitamin, was administered along with capsules of bile salts by mouth. During the last six days very small doses of insulin were added to the glucose infusion, 5 units for each 50 grams of glucose.

On April 17, when anasarca was becoming a problem and the blood proteins were found to be somewhat low, a blood transfusion of 500 cc. was given. Two days later an infusion of 150 cc. of normal human serum of the patient's own blood group was given. This serum had been concentrated so that it represented approximately three times the quantity of the original plasma. This administration was accompanied by a severe chill and temperature of 104°F.



When edema and ascites first appeared the solvent used for the glucose infusion was changed from saline to distilled water because it was feared that too much sodium chloride had been given. However, this resulted in a marked decrease in the urinary output during the following day. The treatment was then changed, normal saline again being used for the glucose infusions. In addition, 300 cc. of 5 per cent sodium chloride was given intravenously for two days in the hope of producing a diuresis. Urine secretion was again restored almost to normal by this means but the edema slowly increased. Then mercupurin in very small amounts, a total of 0.6 cc. in 24 hours, was given in small divided doses in the intravenous infusion. This resulted in an enormous diuresis so that before death the ascites and edema had almost disappeared.

#### COMMENT

I wish now to take up in order certain important points.

(1) There are two *toxic manifestations of sulfanilamide* (3) that interest us in connection with the present case. One is anemia and the other is jaundice.

There are two types of anemia. The first is an anemia which may come on rapidly or slowly without hemoglobinuria and usually without jaundice. It is undoubtedly hemolytic and an increased number of reticulocytes is usually found in the circulating blood. It was this acute benign anemia from which the patient suffered at the end of his first course of sulfanilamide and from which he recovered after the blood transfusion. While the name acute hemolytic anemia is occasionally used for the more severe forms of this benign type of anemia it should, in my opinion, be reserved for the second type.

The second type of anemia, unmistakably an acute hemolytic anemia, comes on abruptly with intense hemoglobinuria, melena, vomiting and jaundice. The jaundice with this anemia is always mild; the really threatening and dangerous manifestation is the hemoglobinuria because that so often leads to the suppression of urine.

There likewise seem to be two types of jaundice. The one comes on with obvious evidences of hemolysis, either the simple benign anemia referred to above or the acute hemolytic anemia. This type of jaundice, of which I have seen nine cases, usually is rather mild and does not show the laboratory manifestations which accompany toxic hepatitis. The other type, of which I have seen three cases, is more severe, shows all the manifestations of toxic hepatitis, and may be accompanied by evidences of hemolysis but frequently (as in the present instance) is not so accompanied.

As to the frequency of these rather severe toxic manifestations of sulfanilamide no accurate statistical data are as yet available. Probably they occur only once in many hundreds of cases. Unfortunately, at present there is no way of predicting or preventing their occurrence.

It is worth noting in this case that sulfanilamide, which had previously produced an acute anemia and had, on that account, been discontinued, was again given to the patient for three days just before operation.

(2) The second point for discussion is the *toxicity of avertin*. I have

seen two cases of mild simple jaundice develop after the use of avertin as an anesthetic for minor operations, such as hernia. Jaundice after avertin is referred to in the literature (4) and, in fact, on account of the similarity of avertin (which is tribromethanol) to chloroform (which is trichloromethane), one might well expect it to occur occasionally.

It is, however, impossible to say in the present case whether the liver atrophy was due to a *combination* of sulfanilamide and avertin. It would be wise in the future when patients have received one known hepatotoxic drug to refrain from the use of an hepatotoxic anesthesia.

(3) The third question is whether the *ultra-violet light* treatment was a contributing factor. It is well-known that persons taking sulfanilamide are especially susceptible to the effect of sunlight, tending to develop skin eruptions when exposed. This has been attributed to the formation of abnormal porphyrins under the influence of the drug. In the present instance the drug was no longer being given, in fact had been discontinued for ten days, when the ultra-violet light was used. It is perhaps a mere coincidence that the jaundice was first noticed shortly after the ultra-violet light therapy.

(4) The next point to which I wish to call attention is the occurrence of a *silent (incubation) period* between the last administration of sulfanilamide or avertin and the appearance of jaundice. This silent period is characteristic of most of the toxic idiosyncrasies of sulfanilamide. It occurs with agranulocytosis, acute hemolytic anemia and jaundice. In all of these there may be a period of anywhere from two days to several weeks between the cessation of the therapy and the onset of toxic manifestations.

In the present case there is an interesting parallelism between the silent period and the pre-icteric period described in the infectious type of acute yellow atrophy of the liver in Bergstrand's monograph (5). Some ten years ago there occurred in Sweden an epidemic of catarrhal jaundice; during the same year there was what practically amounted to an epidemic of acute yellow atrophy of the liver. Bergstrand collected over ninety cases of atrophy in that year. He found that there was a pre-icteric period lasting from ten days to a month during which the liver was usually enlarged (as it was indeed in the present case). It seems that only when the liver damage reaches a certain point does jaundice appear. Bergstrand thinks that it is possible that there may be cases of hepatitis which run their entire course without showing jaundice. In comparing our case with the cases of acute yellow atrophy in the Swedish series, it is also interesting to note that the duration of the jaundice was about the same as in the Swedish cases, namely a month.

(5) The fifth point to which I shall refer is that it is difficult (not to say, impossible) with our present knowledge to make an accurate prognosis, at least in the early stages of hepatic degeneration, or, indeed, of catarrhal jaundice. The symptoms in themselves have no prognostic value; the

mildest cases sometimes go on to acute yellow atrophy and those which start with severe digestive symptoms often recover.

The unusually low blood cholesterol and cholesterol esters, after only one week of jaundice, suggested at the start that this might be a severe case. Pointing in the same direction (and practically clinching the diagnosis) was the steadily rising blood bilirubin curve with the steadily dropping blood cholesterol and cholesterol esters. However, I have seen the same phenomenon occur in cases which ran a benign course and recovered.

The tyrosin test in the urine failed us in the present case. This is hard to explain, as the test is so often found positive in relatively mild cases of the disease; I can only fall back on the general observation that there is no one laboratory test which is infallible in jaundice. The early presence of a positive tourniquet test might perhaps have put us on our guard, suggesting that we were dealing with a case which was likely to run a grave course.

(6) With regard to the *hemorrhagic tendency*, the most significant and interesting factor was the great reduction of blood fibrinogen. This has been reported again and again in parenchymal disease of the liver and, in fact, is the principal evidence that the liver is responsible for the production of fibrinogen. The liver is believed to be at least partly responsible for the production of other blood proteins. Hypoproteinemia, such as was found in the present case, usually occurs in severe liver cell damage and is believed to be the chief cause of anasarca in these cases.

(7) I wish to draw special attention to the severe *abdominal pain* from which the patient suffered. It was intense, colicky, almost continuous, and required the frequent administration of opiates. It only occurred in the last ten days of the patient's life. Bergstrand says that severe pain occurred in a large number of his cases. Actually in one-sixth of his cases exploratory laparotomies were needlessly done in the fear that some other cause for the abdominal pain was present. The mechanism of this severe pain is unknown. Possibly it is due to an acute congestion of the viscera due to back pressure from collapse of the liver.

(8) As to *therapy*, there were a number of questions that arose in the course of this case. The administration of carbohydrates in order to encourage the deposit of glycogen in the liver is the present universally accepted basis of therapy. Because insulin in diabetes causes the deposit of glycogen in the liver, the administration of insulin along with large amounts of carbohydrates has been advocated for patients with jaundice. There has always been some doubt as to the necessity of this because all attempts to show that insulin, in the presence of a normally functioning pancreas, can cause an increased deposit of glycogen in the liver have failed. And there has never been any evidence (such as would be afforded by a high blood sugar) that the pancreas does not produce a normal amount

of insulin in cases of hepatic degeneration. Nevertheless, since insulin, if covered by the simultaneous administration of an excess of carbohydrates, is safe to give, it was given intravenously in the present case—five units of insulin along with fifty grams of carbohydrates.

Another question which arose was the advisability of treating the patient with anti-anemia liver extract. This has been advocated by Richard Bauer (6) on purely clinical grounds for the more severe cases of toxic hepatitis. It has been tried at this hospital in several cases but we have not been convinced definitely that it influences the course of the disease. On the other hand, a mild toxic hepatitis occurs, though rather uncommonly, under continuous treatment with intra-muscular injections of liver extract. We have seen at least a dozen such cases at The Mount Sinai Hospital. (Two cases were present in the wards at the time this paper was being written.) This occurrence has made us hesitate about using liver extract at all in cases where there is already liver damage.

In the treatment of the dropsy, blood transfusion and the injection of homologous human serum in order to elevate the blood proteins had no particular success in the present case. The treatment which did greatly reduce the dropsy was the intravenous administration of mercupurin. This was given very cautiously, less than one cc. in 24 hours by the slow drip method, and was very effective.

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## CALCIFIED PROTRUDED INTERVERTEBRAL DISC<sup>1</sup>

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(*From the Neurosurgical Service*)

During the past few years the importance of protrusion of an intervertebral disc as a causative factor in low back pain, and its attendant disability, has been stressed by many authors. Many relatively large series of cases have been reported. There would be, therefore, little advantage in adding another isolated case report, were it not for the fact that it presents several unusual features. The latter set the case apart as an exception to, rather than an example of, this condition.

### CASE REPORT

*History* (Adm. 435961). A sixty-three year old retired pharmacist was admitted to the Neurological Service on February 7, 1939. He complained of pain in the lumbar region, which he dated precisely from August 28, 1938. While arising from a chair on that day, he felt a sudden severe pain low in the back. It was of such intensity and was so aggravated by walking that he had to remain in bed for the succeeding few days. He then was able to get about but suffered daily with pain which seemed to be mild in the morning and increased in severity as the day progressed. It also at times interfered with sleep. He was most comfortable when in a semi-reclining posture, propped up on pillows, in which position he was able to sleep.

The patient had been retired from active work for seven years because of symptoms referable to his heart. There was no other illness of importance, and no history of trauma to his back.

In January 1939, about a month prior to his admission to the hospital, he began to experience numbness in both legs and paresthesias of both feet. The latter at times was a sensation of heat or cold; at other times it felt like pins and needles. Weakness of the lower extremities appeared soon after the numbness so that at times his knees buckled under him and walking became difficult. There was an associated loss of libido, but no interference with the vesical or rectal sphincters.

*Examination.* The patient appeared older than his years, and presented evidence of a moderate arteriosclerosis. His blood pressure measured 160 systolic and 78 diastolic. There was a brown flat pigmented area about 2 cm. in diameter in the skin just to the left of the fifth lumbar vertebra. The spine was held rigidly and tenderness was noted over the lower lumbar spines. His gait was slow and ataxic. Motor power in the lower extremities was but little impaired. The deep reflexes were lively, the right being a shade more active than the left. Plantar stimulation gave poor response on both sides. The upper abdominal reflexes were normal while the lower and cremasteric reflexes were absent.

Sensation to pin prick was much diminished and at some points absent in the area from the upper third of both thighs anteriorly down, and posteriorly in the area involving both buttocks and thighs. In these same areas, temperature sense was also

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<sup>1</sup> Presented in part at The Mount Sinai Clinical Conference, April 28, 1939.

much diminished. Vibration was not perceived below the iliac crests, while position sense remained intact.

*Laboratory Data.* Manometric studies showed a complete block but the total protein was but little elevated, being 46 mg. per cent on one determination and 68 on another. Other laboratory studies, as well as roentgen examination of the spine, did not yield any significant findings.

*Diagnosis.* Localization from the sensory findings was impossible as the changes followed neither a peripheral nor a true segmental pattern, though they more closely



FIG. 1

FIG. 2

FIG. 1. Roentgenogram showing iodized oil arrested at the lower border of the tenth thoracic vertebra.

FIG. 2. Roentgenogram showing the arrested iodized oil in a lateral view. The arrow points to a calcified mass between the tenth and eleventh thoracic vertebrae.

resembled the latter. The presence of the upper and the absence of the lower abdominal reflexes placed the lesion higher than that which was indicated by the sensory changes.

*Course.* Iodized oil injected into the cisterna magna was completely arrested at the lower border of the tenth thoracic vertebra (figures 1 and 2), but the following day all the iodized oil had descended into the cul de sac.

On March 2, a laminectomy from the tenth thoracic to the first lumbar vertebra was carried out. When the dura was opened the cord was found pushed backward

opposite the lower border of the tenth thoracic vertebra by a mass lying beneath the anterior dura. By retraction of the cord and incision of this dura, the mass was exposed. It was found to be made up of calcified material which was completely removed with a curette. The material removed was reported as calcified intervertebral cartilage.

Except for a temporary increase in weakness of the legs and urinary difficulty, the convalescence was without untoward incident. At the time of his discharge from the hospital on March 28, the power was rapidly improving and sensory disturbances were limited to some hypalgesia in the right thigh and diminished vibratory sense bilaterally. A review of the X-ray plates showed what appeared to be a calcified mass between the tenth and eleventh thoracic vertebrae just at the site of the iodized oil arrest (figure 2).

#### COMMENT

While protrusion of an intervertebral disc is essentially a lesion due to trauma, occurring with greatest frequency in the age groups between twenty and sixty years, an appreciable number of cases are found in older persons and a greater number of cases without a history of trauma.

In a recent review of two hundred cases operated upon at the Mayo Clinic, Walsh and Love (1) pointed out that in all but fifteen cases the protrusion was in the lumbar region. Hence, the site of the lesion in this patient is one of the less frequent ones.

The exaggerated deep reflexes associated with the absent lower abdominal reflexes would immediately place the lesion above the cauda equina, while the dissociation between vibratory and position sense would also point away from a sole root compression. In fact, until the lesion was disclosed at operation there was no thought of a protruded disc; a spinal cord tumor in its true sense was the preoperative consideration. This diagnosis found further support in the presence of an almost complete block as revealed by manometric study of the cerebrospinal fluid, and by the occurrence of a complete, though temporary, arrest of the iodized oil injected into the subarachnoid space.

In the X-ray studies with a contrast medium of the patients with protruded discs, the diagnosis is most often made by deformities in the iodized oil column seen under the fluoroscope and demonstrated by "snap" roentgenograms. In this case the arrest was of a complete and more permanent character. Aside from true tumors, this type of iodized oil picture is noted more frequently in patients with a thickened ligamentum subflavum than with herniated discs.

Calcification of parts of the intervertebral disc both in its normal position and of the herniated portion are described by Schmorl (2) and roentgen photographs are shown but these were made from anatomical preparations. Hampton and Robinson (3) noted the possibility of calcification of a prolapsed nucleus pulposus, but interpreted it as a fragment of a fractured vertebra. Hence the calcification seen in the X-ray studies of this case mark it as an unusual finding. Even here it was a postoperative observation.

It would be pure speculation to discuss the time element in the calcification of the disc—whether it preceded the protrusion or followed it. Since we have no history of trauma there is no way of approximating the time of the protrusion, nor are we completely justified in fixing this at the time of the onset of the symptoms.

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# ANEURYSM OF THE AORTA DUE TO RHEUMATIC FEVER<sup>1</sup>

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Aneurysmal dilatation of the aorta in individuals below the age of 40 is usually syphilitic in origin, for in such young patients atherosclerosis is rarely a factor. However, aortitis and aortic dilatation progressing to aneurysm formation may occasionally occur in rheumatic fever. In 1934 Calvin and Nichamin (1) were able to collect forty-five reported cases of aneurysm of the thoracic aorta in individuals below the age of 18 years. In one-half of these the presence of proved rheumatic endocarditis or myocarditis was established. Such a case is presented in the following report.

## CASE REPORT

*History* (Adm. 377051). E. S., a 27 year old Jewish peddler, was admitted to the Cardiac Clinic in 1937 complaining of increasing dyspnea on exertion for the preceding three years. He also had a feeling of heaviness and occasionally experienced a dull pain in the precordium.

The patient had suffered recurrent attacks of polyarthritides at the ages of 19, 22 and 25 years, each time involving mainly the knee, elbow and wrist joints. With each attack the patient was bedridden for two to three months. A cardiac murmur was discovered after the first attack. From 1936 on, the patient had attended several cardiac clinics for rheumatic cardiovalvular disease. No history or evidence of venereal infection was ever elicited. The patient was married and had three children.

*Physical Examination.* The patient was obese, weighing 196 pounds. He was mildly dyspneic and the neck veins were moderately distended. The heart was markedly enlarged to the left and downward, the apical impulse being palpable in the sixth left interspace in the anterior axillary line. The base of the heart was widened on percussion. The apical heart sounds were partially replaced by a loud, blowing systolic murmur. In the aortic area there were audible a loud, rough systolic murmur and a blowing diastolic murmur which were transmitted downward along the left sternal border to the apex. The cardiac rhythm was regular and the blood pressure was 145 systolic and 0 diastolic. The clinical diagnosis was chronic rheumatic cardiovalvular disease with mitral insufficiency and aortic stenosis and insufficiency.

*Circulatory Studies.* Owing to the presence of increasing dyspnea on exertion and of distended neck veins, it was believed that the patient was developing congestive heart failure, despite the absence of other physical signs pointing to such a condition. This was corroborated by the circulation studies, for the venous pressure was elevated to 20 cm. and rose to 24 cm. on pressure over the right upper quadrant, and the decholin arm-to-tongue time was prolonged to 28 seconds. The vital capac-

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<sup>1</sup> Presented at the Clinical Conference, October 22nd, 1937.

ity was diminished to 3200 cc., which was about 65 per cent of the calculated normal for the patient's height and weight.

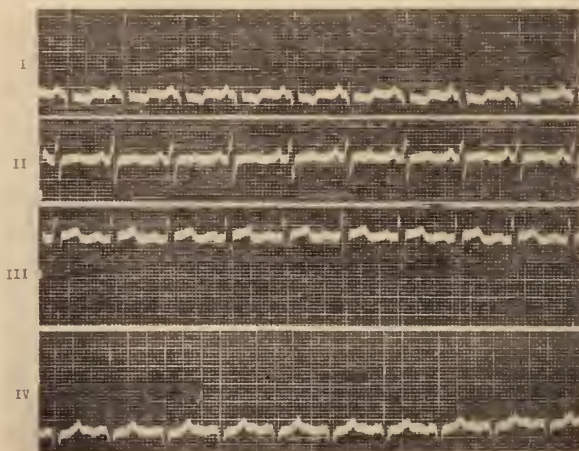


FIG. 1. Electrocardiogram reveals marked left axis deviation, high voltage of the QRS and inversion of the T-wave in lead I, all characteristic of the enlarged left ventricle present in aortic insufficiency.



FIG. 2. Teleoroentgenogram, posterior-anterior view, shows marked dilatation of the ascending and descending thoracic aorta. The left ventricle is enlarged downward and to the left.

*Electrocardiographic Examination.* The electrocardiogram (fig. 1) was typical of advanced left ventricular enlargement, presenting marked left axis deviation, huge voltage of the QRS complex and depression of the S-T segment and inversion

of the T-wave in lead I. This pattern is associated with the aortic stenosis and insufficiency which predominated over the mitral lesion.

*Radiological Examination.* The most interesting finding in this case was revealed by the fluoroscopic examination. As was expected, marked enlargement of the left



FIG. 3. Teleoroentgenogram, right oblique view, shows retrodisplacement of the barium-filled esophagus by the enlarged left auricle.



FIG. 4. Teleoroentgenogram, left oblique view, outlines the dilated ascending arch and descending thoracic aorta. The left ventricle is enlarged posteriorly.

ventricle and moderate enlargement of the left auricle were demonstrated after the ingestion of barium. In addition, there was observed a marked dilatation of the entire thoracic aorta, particularly the ascending portion, which was aneurysmal

in outline. The teleroentgenograms (figs. 2, 3 and 4) corroborated these observations. The roentgenkymogram revealed markedly increased pulsation of the entire thoracic aorta. Correspondence with the other cardiac clinics which the patient had attended revealed that the aortic dilatation had been noted for at least one year, but to a lesser degree.

#### COMMENT

The presence of the very marked involvement of the aorta at first raised a doubt as to the diagnosis of rheumatic heart disease made on admission. Ordinarily such marked aneurysmal dilatation of the aorta would point to a presumptive diagnosis of luetic aortitis and aortic insufficiency, particularly in a patient 27 years of age in whom a marked degree of atherosclerosis of the aorta would be highly improbable. The presence of syphilis, however, could not be established either from the history or on physical examination. Repeated blood Wassermann tests carried out at Mount Sinai and other hospitals were negative on five separate occasions. A provocative Wassermann test was also negative. A spinal tap was performed and the cerebrospinal fluid Wassermann test and the colloidal gold reaction also proved to be negative. We therefore were reasonably certain that the valvular and aortic involvement was not due to syphilitic cardiovascular disease.

The only other plausible explanation was that the aorta was the seat of a rheumatic infection which had resulted in the marked dilatation. Extensive pathological studies including those of Klotz (2) in 1913, and later those of Pappenheimer and von Glahn (3-6), Kugel and Epstein (7), Perla and Deutch (8), and Gray and Aitken (9) have demonstrated that not uncommonly the rheumatic infection may involve the aorta, pulmonary artery and other large arteries. Instances of aortitis and pulmonary arteritis due to rheumatic infection have also been reported in the foreign literature (10-15). Direct infection from the lumen of the artery may produce intimal verrucae, leading to the secondary formation of fibrinous plaques and scarring of the intima. More important probably is the hematogenous spread from the blood stream along the vasa vasorum and the production of an inflammatory process in the adventitia and media, with degeneration of the muscle and elastic fibers. The weakening of the wall of the aorta which results from this inflammatory process may lead to dissection along the media, to diffuse dilatation and ectasia, as in this case, or even to true aneurysm formation.

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## THE NEPHROTIC SYNDROME IN DIABETES<sup>1</sup>

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The patient whose clinical history is presented here illustrates the occurrence of a nephrotic syndrome in diabetes mellitus. The purpose of this report is to draw attention to this not unusual clinical association.

### CASE REPORT

*History* (Adm. 437064). The patient, a 55-year old negress, had been under observation in the diabetes clinic since 1935. Her family history was of no significance. Her past history was negative. There was no history of scarlet fever, kidney disease or of hypertension. She complained of marked loss of weight, moderate polydipsia and polyuria of several months' duration. Five per cent glucose and a trace of albumin were discovered in the urine. Her blood pressure was 158 systolic and 90 diastolic. Her diabetes was mild and readily brought under control on a diet of 120-60-60 with ten units of regular insulin daily.

A tendency to unusually rapid weight gains was noted within the first few months of observation but it was not until 1937, after a rather long lapse in clinic attendance, that the appearance of edema was first observed. At this time she also had shooting pains in the left leg and a sensation of deadness in both hands. She had had swelling of the legs for several months but no dyspnea or precordial pain. There was a hypertension of 190 systolic and 90 diastolic, a tachycardia of 116, and moderate pretibial pitting edema.

In the light of previous experience with similar cases, the cause of the edema was forthwith sought in hypoproteinemia. The blood total protein was found to be 4.4 grams per 100 cc. with albumin and globulin fractions each 2.2 grams per cent. Blood cholesterol was 535 mg. per cent. The urine contained a heavy trace of albumin with some casts and a rare red blood cell.

It was apparent then that the patient presented the clinical and laboratory findings of the nephrotic syndrome as seen in the course of chronic glomerulonephritis. She was referred to the hospital wards for more intensive study and therapy.

*Examination.* The pupils were equal, reacting to light and accommodation. The lungs were negative; there was no evidence of pleural effusion. The heart was not enlarged; regular sinus rhythm; no murmurs; the liver was palpable two finger-breadths below the costal margin. Slight dullness was present in both flanks, with a fluid wave. There was moderate dependent edema. The peripheral pulses were patent. The deep reflexes were equal and active. The blood pressure was 170 systolic and 100 diastolic. The fundi were described by the ophthalmologist as showing slight narrowing of the arteries. The neurological consultant found only slight evidence of peripheral neuropathy, namely, diminution of vibration sense in both lower extremities, pain and touch being only slightly affected.

*Laboratory Data.* Hemoglobin, 63 per cent; red blood cells, 3,900,000; white blood cells, 7,100; normal differential count; blood urea nitrogen, 15 mg. per cent; glucose,

<sup>1</sup> Presented in part at the Clinical Conference, March 24, 1939.

160 mg. per cent; cholesterol, 470 mg. per cent; and total protein, 5.4 grams per cent (albumin 2.6, globulin 2.8). The blood Wassermann reaction was negative. The urine showed from a very faint trace to two plus albumin, the Esbach quantitative test showing as much as two grams of albumin per liter. There was an occasional hyaline cast and a rare red blood cell. The urine concentrated only to a specific gravity of 1.017.

The venous pressure was 5 cm; circulation time, measured by the saccharine method, was 12 seconds. These determinations supported the clinical impression that circulatory failure played no role whatsoever in the production of the edema. The electrocardiogram showed left axis deviation, QRS complex slightly slurred with moderately low voltage, and  $T_1$  isoelectric.

*Course.* Under observation for a period of nineteen days, the patient's diabetes was brought under control on a regime of 150 gm. CHO, 150 gm. protein, and 120 gm. fat, without insulin. The edema disappeared on this diet and bed rest, without the use of diuretics. The albuminuria decreased. The total protein rose to 6.2 gm. per cent, but of this the albumin fraction remained only 2.5 grams.

Because of the ready response to treatment the patient was discharged with the diagnosis of diabetes mellitus and essential hypertension. The edema and hypoproteinemia were thought to be due to malnutrition, caused by strict adherence to a limited diabetic diet.

She remained under close observation in the diabetes clinic and had two subsequent hospital admissions during the next two years. The patient's clinical course was such as to modify the former somewhat optimistic clinical impression as evidence of cardiac and renal failure appeared. Despite faithful adherence to a high protein regime there was a reaccumulation of edema, the low blood proteins persisting, 5.0 gm. per cent (albumin 2.2, globulin 2.8), together with increased blood cholesterol levels, 765 mg. per cent, and profuse albuminuria.

Two further laboratory findings are to be noted. A Congo-red test showed only 35 per cent retention, indicating the absence of amyloidosis. A glucose tolerance test confirmed the presence of moderate diabetes.

The blood pressure tended to rise, reaching 230 systolic and 120 diastolic; marked hypertensive retinopathy with hemorrhages and exudates appeared; there was increasing evidence of cardiac enlargement and insufficiency. In the last few months of observation azotemia set in with a blood urea nitrogen rather rapidly rising to 114 mg. per cent. The patient was discharged from the hospital in a state of suburemia and several weeks later she died in coma.

*Necropsy Findings.* General *anasarca* was present. The *heart* was enlarged, weighing 500 grams. The *lungs* were congested and edematous. The *liver* was congested. The *pancreas* showed marked post mortem autolysis.

The *kidneys* weighed 200 grams each; they were enlarged, greyish with a yellow tinge; the surface was slightly and finely granular, the capsule stripping easily. Cut surface: cortex was somewhat narrowed; cortical markings, indistinct. The large renal arteries were markedly sclerotic. The gross appearance suggested either the large white kidney of glomerulonephritis, or possibly amyloidosis.

*Microscopic Examination.* The normal architecture of the cortex was disrupted. Practically all the glomeruli were involved in some degree by fibrosis or hyalinization. Many glomeruli showed marked capsular fibrosis. Glomerular tufts showed varying grades of fibrosis often enclosing discrete areas of hyaline. Other tufts were completely hyalinized. There was no adhesion between tuft and capsule; no proliferation of tuft epithelium, or cellular crescents.

Marked sclerosis of the smallest arteries and arterioles was present. Many of the afferent arterioles showed advanced thickening, hyalinization and narrowing of lumina. In some places there were fat cells in their walls. The medium sized or

interlobular arteries were less affected, but in some instances showed fairly marked intimal thickening. There were several scattered foci of mononuclear cells. The tubules showed marked desquamation of epithelium. When still apparently intact, the epithelium was flat and presented no unusual features. Many of the tubules showed almost complete post mortem autolysis.

Sudan stain showed scattered fat deposits in only a moderate amount. These were in the glomeruli, small arteries and arterioles, and to some extent in the tubules. The amyloid stain was negative. Examination with the aid of the polariscope revealed only a small number of doubly refractile bodies, not increased above normal.

The anatomical findings pointed to advanced arteriosclerosis with no evidence of glomerulonephritis.

#### COMMENT

Interest in this case derives from the clinical suspicion that the association of diabetes and severe renal damage, with the production of the nephrotic syndrome, is more than sheer coincidence. Experience suggests that the diabetes and the renal picture bear some relation to each other. A survey of The Mount Sinai Hospital records from 1933 through 1938 reveals that of 205 patients discharged with the diagnosis of chronic nephritis or nephrosis only 14 were diabetic. But of these, 11 presented a nephrotic picture. Two additional cases have been observed, so that 13 cases illustrating this syndrome have so far been collected and studied (see table 1).

The following clinical features of these cases deserve special emphasis:

1. *Age Group.* Twelve of the thirteen patients were over 45 years of age.
2. *Type of Diabetes.* In all but the youngest case it was mild, requiring little or no insulin for adequate control.
3. *Chronologic Relationship of the Diabetes and the Renal Syndrome.* This is difficult to state categorically, for both conditions are characterized by insidiousness of onset. Insofar as this can be known, the diabetes preceded the renal disease by from five to twenty years in six cases, and by from one to five years in three cases. Of the remaining four patients, the diabetes was discovered several months before the renal disease in two, but in two others the symptoms and signs of the renal condition developed a few months before the discovery of the diabetes.
4. *Peripheral Neuropathy.* One of these patients presented these changes to a severe degree, amounting to pseudotabes; in two others the evidence of peripheral nerve involvement was slight.
5. *Hypertension.* A systolic blood pressure of 190 or more, with a diastolic level of about 100, was observed in twelve of the thirteen patients. In the youngest patient the average level was 145 systolic and 100 diastolic but rose to 210 systolic and 128 diastolic during an episode of hypertensive encephalopathy.
6. *Cardiac Failure.* Some degree of heart failure was present in nine out of the thirteen patients either coexistent with the nephrotic picture or appearing later.
7. *Azotemia.* Some degree of nitrogen retention was present in eight of these cases and progressed to uremia in five, all of whom died.
8. *Prognosis.* This appears to be very unfavorable. Seven of the thirteen cases here reported died within two to three years of



TABLE 1  
*Diabetes and the nephrotic syndrome*

CASE	AGE	SEX	DURATION OF DIABETES	INSULIN NEEDED units	RENAL DISEASE DURATION	BLOOD PRESSURE	FUNDUS CHANGES	CARDIAC FAILURE	AZOTEMIA	POLYNEURITIS	Hgb.	URINE				TOTAL PROTEIN, ALBUMIN, GLOB. ULIN	CHOLESTEROL	SUGAR	REMARKS
												Alb.	Gm./l.	Rbc.	Casts				
1 B. S.	54	F	7 years	25-30	4-16 months	210/90	4+	±	1-4+	0	74-43	4+	6.6	0	1+	4.8, 2.4, 2.4	775	265	Death in uremia 3 years after onset
2 S. A.	50	F	20 years	15-30	2 years	180/90	2+	2+-4+	2+	4+	60	3+		±	1+	5.6, 3.2, 2.4	675	310	Death in heart failure 3 years after onset
3 M. S.	49	M	10 years	0-20	7 months	200/110	2+	1+	1-3+	±	80	3+	3.0	±	1+	4.2, 1.8, 2.4	500	155	Progressive azotemia
4 A. F.	44	M	15 months	0-15	6 months	220/140	4+	1+	2-4+	2+	62	3+		0	3+	5.1, 2.9, 2.2	650	192	Death (heart failure, uremia) 2 years after onset. Post Mortem: Glomerulonephritis
5 R. J.	56	F	12 years	0-15	15 months	200/110	4+	2+	±	1+	72	4+	8.5	2+	1+	4.4, 2.2, 2.2	750	175	Death, uremia 2 years after onset. Post Mortem: Nephrosclerosis
6 F. G.*	55	F	2 years	0-35	Several months	200/105	3+	0-3+	0-4+	±	63	2+	2.5	1+	1+	4.4, 2.2, 2.2	535	260	Progressive cardiac and renal failure. Post Mortem: Nephrosclerosis
7 S. K.	73	M	5 years	0	2 years	200/100	3+	0	0	0	70	2+		3+-1+	2+	5.2, 3.1, 2.1	410	230	Death in uremia and cardiac failure. Post Mortem: Nephrosclerosis
8 M. S.	50	M	†	0	4 months	180/130	3+	2+	0-4+	0	88	3+	3	1+	1+	4.5, 2.2, 2.3	375	145	Marked nephrotic picture, no heart failure
9 S. C.	48	F	2 months	0	6 months	200/90	2+	0	0	0	70	3+	6	±	3+	4.9, 2.8, 2.1	625	180	Complicating congestive failure. Beginning azotemia
10 J. G.	46	F	9 years	0-30	1 year	210/110	2+	3+	1+	0	80	3+	4	0	3+	4.6, 1.9, 2.7	500	200	Death from lobar pneumonia. Post Mortem: Nephrosclerosis
11 B. G.	60	F	10 years	20	3 years	240/116	2+	1+	0	0	62	3+		0	±	4.8, 3.2, 1.6	830	215	Quite marked edema; no cardiac failure
12 C. C.	66	M	6-7 years	0	2 months	212/112	±	0	0	0	72	4+		±	1+	4.8, 3.4, 1.4	370	280	Typical nephrotic picture with severe diabetes
13 B. G.	19	M	4 years	60-85	2½ months	152/100	0	0	0	0	100	3+	5.5	±, 1+	1+	4.9, 1.8, 3.1	1000	300	

\* Case here presented in detail.

† Diabetes discovered in hospital.

the onset of the renal manifestations, death in six of these being due to uremia, cardiac failure, or both.

The clinical characteristics of these cases differ from those of the nephrotic phase of chronic glomerulonephritis as ordinarily observed among non-diabetics—the nephrotic picture is less striking, the albuminuria not so massive, and the reduction in blood proteins not so marked. There is a greater frequency of marked hypertension and, probably as a corollary to this, a much more common association with cardiac failure. The fundus changes are much more severe, probably because the combination of hypertension and diabetes act together to cause severe vascular damage.

Of 93 non-diabetic patients with the nephrotic syndrome observed at this hospital during 1933 through 1938, only ten were 45 years old or more. It therefore appears that one out of every two patients with the nephrotic picture in this advanced age group is likely to be a diabetic. It is interesting that only the youngest case in this series (Case 13), appears to be clinically indistinguishable from the typical nephrotic syndrome as seen in the non-diabetic.

The experience with this small group of patients would indicate that the prognosis of this condition is poor as the nephrotic picture merges progressively with that of uremia and heart failure. A latent period following the nephrotic syndrome is known to occur in the course of occasional cases of the nephrotic phase of glomerulonephritis in the non-diabetic. So far no instance of this has been observed in the diabetic group.

The clinical behavior of these patients raises the question whether the diabetic cases are pathogenetically distinct from the nephrotic phase in the course of a glomerulonephritis without diabetes. Beside the case here presented in detail, four other such patients have come to autopsy. The kidneys in these four cases, however, were not all studied with special stains or techniques (e.g., polariscopically, for doubly refractile bodies) to aid in an exact determination of the type of lesion present. Nevertheless, a review of the microscopic sections leads to the following preliminary conclusions: In three of the cases (Cases 5, 8 and 11) the renal lesion is an advanced stage of nephrosclerosis. As in the case presented, the kidneys are not contracted, weighing 180 to 200 gm., this increase in size not being altogether explicable on the basis of the microscopic findings. In case 4 a true subchronic glomerulonephritis is the chief lesion, some degree of vascular disease being also present. In none of the kidney sections studied is there conspicuous tubular fat deposition or vacuolization of the tubules to suggest the glycogen tubular degeneration (Armanni-Ebstein) known to occur in diabetes.

#### DISCUSSION

A survey of the literature reveals only meager references to the association of a nephrotic syndrome or of chronic progressive renal disease with diabetes. The occurrence of edema in the course of diabetes has been

remarked, but almost always it appears to have been the result of rigorous starvation therapy, or it appeared in the course of recovery from severe ketosis, particularly after the application of drastic sodium bicarbonate therapy (5).

The more frequent incidence of hypertension among diabetics than in the general population has often been the subject of comment and is now a generally accepted fact (6). That diabetes and hypertension are often associated with an unusual albuminuria has been remarked by Fishberg (1). "Cases (of essential hypertension) complicated with diabetes often have large quantities of albumin in the urine, which is of no special prognostic significance. . . ." In the most recent edition of his book, however, he adds: ". . . in exceptional cases, the albuminuria is sufficiently massive to produce hypoproteinemia and consequent edema—a true nephrotic syndrome" (2). From the clinical data presented in this report, it is apparent that the prognosis of such cases is quite definitely poor. The significance of a heavy albuminuria in the hypertensive diabetic cannot therefore be altogether ignored.

The occurrence of a nephrotic syndrome in the course of diabetes has been previously noted by Kramer (4) who wrote: "The element of nephritis must be considered as a possible explanation of the incidence of hypertension in diabetes. When . . . a diagnosis of nephritis is warranted, the clinical picture is usually one of the tubular type, and often not unlike that of nephrosis."

Specific reference to the clinical group here described is to be found in a paper by Kimmelstiel and Wilson (3) on certain aspects of renal pathology. They offer brief clinical abstracts of several cases, the clinical and laboratory features of which are similar to those which form the subject of this report. They too find the kidney lesion to be that of severe nephrosclerosis, although they ascribe special significance to the occurrence of marked "hyaline thickening of the intercapillary connective tissue of the glomerulus," which they call "intercapillary glomerulosclerosis." They remark also upon the increased size of the kidneys which obscures the usual gross appearance of advanced arteriolosclerosis.

It is not at present possible to explain altogether the unusual proneness of the middle-aged, mild, hypertensive diabetic to the development of the nephrotic syndrome. It is evident that it cannot be ascribed simply to dietetic restriction, for in the cases so far observed there appears to have been an adequate protein intake. In one instance (Case 2) the clinical picture of massive edema, cardiac failure and severe polyneuritis suggested the possibility that Vitamin B<sub>1</sub> deficiency played a role in the development of the syndrome. However, the oral administration of large amounts of B-complex in that case, and intravenous injections of thiamin chloride in high dosage in case 12 failed to result in any clinical improvement. Furthermore, the major factor of renal failure cannot be accounted for on the basis of dietary deficiency of any kind.

In severe and grossly uncontrolled diabetes excessive protein catabolism, as indicated by a negative nitrogen balance, might result in defective plasma protein synthesis. However, in only one of the patients (Case 2) was the diabetes severe enough and uncontrolled for long enough periods to suggest that this mechanism might explain the development of the nephrotic syndrome.

The subsequent clinical course of these cases is of importance to an understanding of the pathogenesis of this syndrome. The rapid progression of renal insufficiency indicates that, as in non-diabetics, the nephrotic picture is an index of severe renal damage. According to the post mortem observations so far available, the renal pathology in these cases is principally vascular in nature. It is therefore suggested that the nephrotic syndrome, always a striking clinical picture, has served to attract attention to an observation of some practical importance, namely, that in the presence of diabetes the usual clinical course of hypertensive cardiovascular disease or nephrosclerosis may be complicated by a severe renal damage with the development of a nephrotic syndrome and an ultimate termination in uremia. The precise mechanism is obscure by which the diabetes influences the pathogenesis of the renal lesion so as to produce the clinical sequence of events herein described.

#### SUMMARY

The clinical history and the post mortem observations are presented in a case illustrating the occurrence of the nephrotic syndrome in diabetes. Clinical data on twelve additional similar cases are tabulated. In four of five such cases the renal pathology has been found to be vascular and not inflammatory in origin. Particular attention is drawn to the fact that the development of the nephrotic syndrome in the hypertensive diabetic is indicative of a poor prognosis.

Grateful acknowledgement is hereby made to the Montefiore Hospital and to the Office of the Chief Medical Examiner of New York City for permission to study autopsy material and clinical records. The writer assumes full responsibility for the interpretation of this material.

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## CHEMICAL STUDIES ON MOCCASIN VENOM

### II. DIALYSIS AND ATTEMPTS AT FRACTIONATION OF THE HEMORRHAGIC AND HEMOLYTIC COMPONENTS

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(From the Division of Laboratories)

In a previous communication we reported the effects of heat, various hydrogen ion concentrations in the range of pH 3 to 11, and of shaking with chloroform on the hemorrhagic and hemolytic components of the venom of the water moccasin snake (*Ancistrodon piscivorus*) (1). It was found that both of these toxic components were quite unstable at higher temperatures and at the more extreme pH values. It was also demonstrated that, after extraction of an aqueous venom solution with chloroform, both the hemorrhagin and hemolysin remained in the aqueous solution; none could be detected in the lipid fraction. These findings supported the hypothesis that both principles were attached to proteins or substances related to proteins, as has been reported in the case of the hemolysins of *Bothrops* (2), cobra (3), and *Daboia* (4) venom. The present report embodies studies on the effects of dialysis and of precipitation with different concentrations of ammonium sulfate and with alcohol and acetone on the hemorrhagin and hemolysin of moccasin venom.

#### EXPERIMENTAL METHODS

*Tests for Hemorrhagin and Hemolysin.* The qualitative assay for hemorrhagin was carried out by means of the intradermal venom test on rabbits as described before (1, 5). The concentrations of the test solutions always corresponded to a 0.1 per cent native venom solution, unless otherwise specified. This test was satisfactory for qualitative estimation, but, in contradistinction to a report of Pratt-Johnson (6),<sup>1</sup> it was not considered a good method for quantitative titration. Because there is a great variation in the amount of hemorrhage elicited in rabbits, following intradermal injection of small amounts of hemorrhagin, a definite threshold value could hardly be computed, unless a very large number of animals were used.

The quantitative titration of the hemorrhage-producing principle was carried out with chick embryos, as previously reported (1), because the hemorrhage elicited was more constant. Serial twofold dilutions of the solution to be titrated were prepared and each dilution was applied to five

<sup>1</sup> Pratt-Johnson used guinea pigs.

chick embryos. The titer was computed from the mean of the dilutions at which positive and negative reactions were obtained.<sup>2</sup>

The hemolysin was assayed qualitatively by means of blood plates, as previously described (1). The concentration of the test solutions always corresponded to a 0.5 per cent native venom solution, unless otherwise specified.<sup>3</sup>

*Analytical Steps.* Total solids were determined by transferring an aliquot part of the sample into a tarred aluminum dish and drying to constant weight in an oven at 100–105°C. Duplicates were always run. They checked within 0.3 mg.

Nitrogen determinations were carried out according to the micro-Kjeldahl method of Pregl, as modified by Parnas and Wagner (8). The receiving flask contained 5 cc. of a 4 per cent boric acid solution, as suggested by Winkler (9); the ammonium hydroxide could be titrated directly in this mixture with N/70 HCl (methyl red as indicator). Duplicates were always run. They usually checked within 1 to 3 per cent.

#### RESULTS

*Dialysis of Native Venom.* Dialysis was carried out in the ice box<sup>4</sup> against distilled water, using cellophane "300" as membrane material. The water outside the bag was changed twice daily. Dialysis was considered to be finished after five to six days.

When a solution of native venom was subjected to dialysis under these conditions, about one-half of the original dry weight passed through the membrane. This substantiates findings of Micheel and Jung (10). The half which was retained inside the bag could be divided into two fractions. About one-fifth of it was precipitated during dialysis; this sediment, insoluble in salt free water, could be separated from the supernatant liquid by centrifuging. The Kjeldahl nitrogen content of native venom and of its water soluble fraction did not differ very much (14.0 against 14.4 per cent); the water insoluble fraction contained 16 per cent nitrogen. *Table 1* shows a summary of these results.

The fractions obtained by dialysis were tested for their hemorrhagic and hemolytic activities. The results are given in *Table 2*. The hemorrhagic principle did not pass through the membrane to any extent. The two non-dialysable fractions had about the same content of hemorrhagin

<sup>2</sup> 3 positive reactions out of 5, "positive." 2 positive reactions out of 5, "negative."

<sup>3</sup> After the studies reported in this paper had been completed, we found that two different hemolytic components were present in moccasin venom (7). Only one of them, however, later designated as hemolysin A, gave the reaction on agar blood plates under the established conditions (1). Only this hemolysin A is discussed in our first (1) and the present reports.

<sup>4</sup> Only the first experiments were carried out at room temperature (*Tables 1 and 2*).

per gram, as far as could be seen from these qualitative tests. The dialysate, after concentration *in vacuo* at 30-35°C., gave a negative reaction for hemorrhagin, when tested in corresponding dilutions. Only in much higher concentrations, containing about twenty times as much solid mat-

TABLE 1  
*Dialysis of moccasin venom; total solids and nitrogen content*

FRACTION	DRY WEIGHT	PER CENT OF ORIGINAL NATIVE VENOM (DRY BASIS)	PER CENT TOTAL NITROGEN (DRY BASIS)
	<i>mg.</i>		
Nondialysable			
(a) Total.....	152.7*	48.8*	
(b) Water soluble fraction ..	128.0	40.9	14.0
(c) Water insoluble fraction..	24.7	7.9	16.0
Dialysate.....	159.6*	51.2*	
Native venom.....	312.3	100.0	14.4

\* Calculated.

TABLE 2  
*Dialysis of moccasin venom; qualitative assay for hemorrhagin and hemolysin*

FRACTION	HEMORRHAGIN CONTENT			HEMOLYSIN CONTENT	
	Total solids	Intradermal venom test*		Total solids	Reaction on† agar blood plate
		Rabbit A	Rabbit B		
Nondialysable					
(a) Total.....	0.42	+++	+++	2.10	++++
(b) Water soluble fraction ..	0.36	+++	++	1.80	+++
(c) Water insoluble fraction..	0.07	—	—	0.35	++
(c') Water insoluble fraction, concentrated. ....	0.35‡	++	++	1.40§	+++
Dialysate.....	0.45	—	—	2.25	—
Dialysate, concentrated .....	9.00§	++	+	9.00§	trace
Native venom (control).....	0.87	++++	++++	4.35	++++

\* Degree of skin reactions is indicated as follows: —, no reaction; +, redness; ++, weak purpura; +++, moderate purpura; +++++, deep purpura or necrosis.

† Degree of hemolysis estimated arbitrarily.

‡ Concentration corresponding to a 0.5% native venom solution.

§ Concentration corresponding to a 2.0% native venom solution. Otherwise concentrations of test solutions as stated above (p. 271).

ter, did the dialysate show a weak to moderate hemorrhagic effect. The skin reaction elicited by the concentrated dialysate had an appearance slightly different from those produced by other venom fractions. The sites of injections showed a less purple ecchymosis, but a more marked

necrosis. It is not known whether two different chemical units were responsible for these different hemorrhagic effects.

Quantitative determinations of the hemorrhagin content, carried out by means of the chick embryo, gave usually a titer of  $2400 \pm 800$  for undialysed native moccasin venom. Thus, one gram of untreated venom contained usually  $2.4 \times 10^4$  hemorrhagic units, as defined in our first paper (1). The titer did not vary much for different lots of venom, unless old samples were used.

The hemorrhagin titer for dialysed venom varied between 600 and 2400, the average being 1200. Apparently about one-half of the hemorrhagic activity was lost during dialysis. This loss in activity paralleled the loss of solid matter which was also about 50 per cent (*Table 1*).

The hemolysin was retained within the membrane during dialysis; it was found in both nondialysable fractions. The blood plate method did not allow a quantitative determination. The dialysate, after concentration *in vacuo* at 30–35°C., did not have any hemolytic effect on blood plates.

*Precipitation with Ammonium Sulfate.* Fractional precipitation of moccasin venom with ammonium sulfate was carried out as follows: To 10 cc. of a 2 per cent solution of native venom, solid ammonium sulfate was added with stirring to make a 0.1 saturated solution. No precipitation occurred. More ammonium sulfate was then added in steps of additional 0.1 saturation. When, at 0.4 saturation the first definite precipitation occurred, the mixture was allowed to remain at room temperature for one hour, and then centrifuged. The supernatant liquid was removed, its volume measured, and sufficient ammonium sulfate was added to bring it to 0.5 saturation. This procedure was repeated until 0.8 saturation was reached. Definite precipitations occurred at 0.4, 0.5, and 0.6 saturation. Each precipitate, after having been washed with an ammonium sulfate solution of corresponding concentration, was dissolved in 10 cc. of distilled water. The solutions of these precipitates, as well as the supernatant liquid of the slight precipitate, formed at 0.8 saturation, were tested qualitatively for their hemorrhagin and hemolysin content.

The results of the assays are shown in *Table 3* which summarizes several experiments. As far as can be estimated from these qualitative tests, the hemorrhagic and hemolytic components were found for the most part in the globulin fraction. The major part of both principles was precipitated at 0.4 saturation, successively less at 0.5 and 0.6 saturation.

The supernatant liquid at 0.8 saturation was dialysed before being tested for its biological activities. It did not show any hemorrhagic or hemolytic effect when assayed under usual conditions; only at a concentration twenty times as great, a weak to moderate hemorrhagic activity could be demonstrated (*Table 3*). This supernatant liquid, however, still showed the antihemorrhagic effects of the venom, as demonstrated by its ability to produce in rabbits a refractory state as far as the Shwartzman



phenomenon was concerned (5, 11, 12). It was also found to be effective in controlling certain hemorrhagic diseases in humans (13).<sup>5</sup>

A definite purification of the antihemorrhagic principle was accomplished in this way. Although some of its therapeutic potency was lost, it was found that about 98 per cent of the solid matter of the native venom had been removed by precipitation and dialysis. The total nitrogen

TABLE 3

*Fractionated precipitation of moccasin venom with ammonium sulfate; qualitative assay for hemorrhagin and hemolysin*

FRACTION	SATURATION WITH AM- MONIUM SUL- FATE	HEMORRHAGIN CONTENT; INTRADERMAL VENOM TEST		HEMOLYSIN CONTENT; REACTION ON AGAR BLOOD PLATE	
		Rabbit A	Rabbit B	Plate A	Plate B
Redissolved precipitate.....	0.4	+++	+++	++	++
Redissolved precipitate.....	0.5	+++	++	+	++±
Redissolved precipitate.....	0.6	++	+	trace	—
Supernatant liquid.....	0.8	—	—	—	—
Supernatant liquid, concen- trated 20 times.....	0.8	++	+	trace	—
Native venom (control).....		++++	++++	++++	++++

TABLE 4

*Precipitation of moccasin venom with alcohol and acetone; qualitative assay for hemorrhagin and hemolysin*

PRECIPITANT	RATIO OF PRECIPITANT TO 2% VENOM SOLUTION	HEMORRHAGIN CONTENT; INTRADERMAL VENOM TEST		HEMOLYSIN CONTENT; REACTION ON AGAR BLOOD PLATE	
		Supernatant liquid	Precipitate	Supernatant liquid	Precipitate
Alcohol.....	2:1	—*	+++		
Alcohol.....	3:1	+†	+++	—	+++
Acetone.....	1:1	—	++++	trace	+++±
Acetone.....	2:1	—	++++±	—	+++
Control (native venom).....		++++		++++	

\* Concentration corresponding to a 2% native venom solution.

† Concentration corresponding to a 10% native venom solution. Otherwise, concentrations of test solutions as stated above (p. 271).

content of this fraction was about 5 per cent<sup>6</sup> as against 14.4 per cent in native venom (dry basis). The biuret test, strongly positive for native venom, was practically negative. The Molisch reaction, on the other

<sup>5</sup> The experiments involving the Schwartzman phenomenon and clinical results obtained with this fraction will be published later.

<sup>6</sup> The nitrogen was probably partly derived from ammonium sulfate not completely removed by dialysis.

hand, which was very weak for native venom, was distinctly stronger. Apparently, the protein content of this fraction was much lower than that of native venom, its carbohydrate content relatively increased.

*Precipitation with Alcohol and Acetone.* Ten cubic centimeters of 95 per cent alcohol were added to 10 cc. of a 2 per cent native venom solution with stirring and cooling to  $-5^{\circ}\text{C}.$ ; a white precipitate resulted. After stirring for 10 minutes, the mixture was immediately centrifuged. The sediment was dissolved in 10 cc. saline. The alcoholic supernatant liquid was evaporated to dryness *in vacuo* under nitrogen, at 30 to  $35^{\circ}\text{C}.$

The residue, which was only a small fraction of the total venom used, was also dissolved in 10 cc. saline. Similar experiments were carried out using 15 cc. alcohol, and with different amounts of acetone.

The results of these experiments are summarized in *Table 4*. Qualitative assays indicated that practically the entire hemorrhagic and hemolytic activities were precipitated by alcohol and acetone, as far as could be estimated from these tests. Apparently, the hemorrhagin and hemolysin were not destroyed by treatment with these solvents at  $-5^{\circ}\text{C}.$  for a short time. The reactions of the redissolved residues of the evaporated supernatant liquids were negative for hemorrhage and hemolysis. Only in one case in which the test solution corresponded to a 10 per cent native venom solution instead of the usual 0.1 per cent, was a weak hemorrhagic activity found.

#### DISCUSSION

Native moccasin venom was found to consist largely of proteins or substances related to proteins. The pseudo-crystalline crude venom contained about 14 per cent nitrogen. In 2 per cent solution, it gave a positive biuret and xanthoproteic reaction, was coagulated by heat, precipitated by tannic acid, trichloroacetic acid, ethyl alcohol, acetone and by 0.3 to 0.6 saturation with ammonium sulfate. About one-half of its dry weight was not dialysable through cellophane, "300." The content of carbohydrates and lipoids was very small, as far as could be estimated qualitatively.

There are reports in the literature indicating that toxic components of snake venoms have been obtained in a form free of nitrogen, e.g. the neurotoxins of cobra, *Crotalus* and *Bothrops* venom (14, 15). These findings, however, could not be substantiated by Micheel and co-workers (10, 16), Tetsch and Wolff (17) and Wieland and Konz (18). Usually, the toxic constituents of snake venoms have been found associated with proteins or related substances (19); e.g., the hemolysins of *Bothrops* (2), cobra (3) and *Daboia* (4) venoms have been obtained in protein or proteose fractions. The hemolytic component of moccasin venom has not been previously investigated, nor the hemorrhagic component of any snake venom.

The experimental results reported in the preceding pages and in our first publication (1) suggest that the hemorrhagin and hemolysin of moccasin venom are proteins, or are associated with proteins. Practically no hemorrhagic or hemolytic activity was associated with the venom lipoids or carbohydrates, or with dialysable venom constituents of smaller molecular size. After the studies reported in this communication had been completed, we found another indication for the protein nature of the hemorrhagin and hemolysin of moccasin venom (7). Their electrophoretic behavior showed that both of them were amphoteric.

Apparently different in nature from these two constituents, the anti-hemorrhagic principle of moccasin venom was found, partially purified, in the dialysed supernatant liquid of a native venom solution precipitated at 0.8 saturation with ammonium sulfate. This fraction was free of hemolysin, and its hemorrhagin content was very small. In clinical use it was found to be somewhat less effective than native venom, as far as the control of certain hemorrhagic diseases (13) was concerned. However, the undesired allergic skin reactions, found after injection of native venom, did not develop in the great majority of cases after injection of this fraction, probably because of its low protein content. Therefore, it proved very useful in cases difficult to desensitize (20).

#### SUMMARY

1. Moccasin venom contains about 14 per cent nitrogen; it consists largely of proteins or related substances. During dialysis, about one-half of the dry weight is retained by cellophane.

2. Both the hemorrhagin and hemolysin were found associated with protein fractions. Both are practically nondialysable through cellophane; both are precipitated by alcohol, acetone or ammonium sulfate at 0.3 to 0.6 saturation.

3. The antihemorrhagic principle in a native venom solution is partially purified and separated from hemorrhagin and hemolysin by precipitating most of the proteins at 0.8 saturation with ammonium sulfate.

This work was done with the technical assistance of Edward Weissbard.

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## CLINICAL PATHOLOGICAL CONFERENCES

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, November 16, 1939*

### Miliary Tuberculosis

*(From the Medical Service of Dr. George Baehr)*

*History* (Adm. 426563; P.M. 10851). *First Admission.* The patient was a twenty-eight year old colored male who entered the hospital because of cough, fever and expectoration. Three months before admission he had had diarrhea. At that time he was in Spain as a member of the Abraham Lincoln Brigade. Eighteen days before re-entry into this country he developed an upper respiratory infection which persisted. Four days before admission he had a severe headache which kept him awake all night. Since then he had felt feverish, and had had a severe cough with the expectoration of scanty, thick, greenish sputum. There had been no chest pain or hemoptysis. There was no previous history of any pulmonary disease. There was no familial history of, or exposure to, tuberculosis.

*Examination.* He was well-developed and appeared acutely ill. Temperature was 104.6°F.; pulse, 120 per minute; respirations, 30 per minute. The sclerae were suffused. Over the left lower lobe, there were dullness, diminished breath sounds, absent fremitus, and distant voice sounds which were increased in pitch. Only a few râles were audible. The rest of the lung fields were clear. The heart examination revealed no abnormalities. The blood pressure was 100 systolic and 60 diastolic. There was no clubbing or cyanosis. Neurological examination was negative.

*Laboratory Data.* The hemoglobin was 102 per cent (Sahli). The white blood cell count was 8,200 per cu. mm. (64 per cent polymorphonuclear leucocytes, 30 per cent lymphocytes and 6 per cent monocytes). Urine analysis showed a trace of albumin and the presence of an occasional white cell. Sputum typing did not reveal any pneumococci. Blood culture was negative. Roentgen examination of the chest showed the presence of an effusion at the left base. Von Pirquet test was strongly positive. Repeated examinations of the sputum for acid-fast bacilli were negative.

*Course.* Physical signs of fluid at the left base continued to increase. Another roentgen examination of the chest, four days later, showed that the pleural effusion on the left now occupied two-thirds of the left pleural cavity. A thoracentesis was performed and 1000 cc. of straw-colored fluid was removed. The specific gravity of this fluid was 1.018; there were 600 white blood cells per cu.mm., all mononuclear cells; culture of this fluid was negative; no acid-fast bacilli or tumor cells were demonstrated. The fluid was inoculated into a guinea pig. Fever persisted throughout his seven week stay, but gradually became less marked, so that at the time of discharge the temperature was sub-febrile. Because of the race of this patient, the relative leucopenia, the monocytosis, the presence of a sterile pleural

effusion containing all mononuclear cells, and the strongly positive von Pirquet reaction, the diagnosis was considered to be tuberculous pleural effusion. He was therefore discharged to a sanatorium.

*Second Admission.* Six weeks after his discharge he was re-admitted to this hospital. He had been in good health until one week prior to admission, at which time he developed fever, headache and lethargy.

*Examination.* The patient was moderately stuporous and incontinent. The head was somewhat retracted. There was moderate blurring of the right optic disc and blurring of the nasal margin of the left disc. The fundal veins were somewhat full. Firm axillary nodes were palpable. There were moderate dulness and diminished breath sounds at the left base. Neurological examination revealed marked nuchal rigidity, bilateral Kernig sign, left Brudzinski; the deep reflexes were hyperactive throughout; bilateral Babinski and confirmatory signs were elicited.

*Course.* In view of the definite signs of meningeal involvement, a lumbar puncture was performed. The fluid was clear and colorless. The initial pressure was 360 mm.; the Pandy reaction was positive; the cell count was 200 per cu.mm., 90 per cent lymphocytes. Examination of the sediment of the spinal fluid revealed the presence of acid-fast bacilli. The chemistry of the spinal fluid showed: sugar, 17 mg.; chlorides, 585; total protein, 141 mg. The tryptophane reaction was positive. At this time, the report on the guinea pig that had been inoculated on the patient's previous admission was positive for tuberculosis. The patient remained stuporous, the temperature continued to be elevated, and he died seven days after his second admission.

*Necropsy Findings.* There were numerous, small miliary tubercles in the *lungs*, *liver*, *spleen* and serosa of the *stomach*. A tuberculous basal meningitis was also present, and this was the cause of death. The *pleura* over the left lung was adherent and strikingly thickened as a result of caseous pleuritis. The hilar *lymph nodes* were markedly caseated. Fluoroscopy of the lungs, post mortem, failed to demonstrate any calcified lesion.

*Comment.* *Dr. Klemperer:* The interesting feature of this case is that it represents a primary stage of tuberculosis. The primary infect was probably just beneath the left pleura with subsequent direct involvement of the pleura. Another possibility is that the pleural infection resulted from a lymphogenous spread from the primary complex in the caseous hilar nodes. The infection was progressive and eventually there resulted blood stream invasion and a miliary spread of the tuberculosis.

*Dr. Baehr:* Rapid progressive tuberculous infection, and this case is an example, is more characteristic of the colored race. The death rate from tuberculosis is four to five times greater in the colored race. The colored people usually either have no tuberculosis or a rapidly progressive disease process. As a rule, their resistance to tuberculous infection differs materially from that of white people. Hence, the course of the disease is more apt to be that of a virulent infection with rapid spread giving rise to symptomatology early in the course of the disease. In the white race, the disease is usually one of slower development and gradual progress. For this reason, the chronic phthisis of the white man is a greater menace to others, because he may be ambulatory for many years, sometimes for a

lifetime, and may die eventually of some other disease. During this long period he may continue to expectorate tubercle bacilli and expose many more persons to infection than would a colored man with a rapidly fulminating process.

Reported by *Max Ellenberg, M.D.*

*Wednesday, November 23, 1938*

### Myocarditis in Diphtheria

*(From the Pediatric Service of Dr. Bela Schick)*

*History* (Adm. 424529; P.M. 10804). The patient, a six year old male, was admitted to the hospital for the first time on May 24, 1938. His past history and family history were not significant. Three and one-half weeks before admission the child vomited and had a temperature of 102°F. The mother noted that the throat was red and the tonsils inflamed. The next day a white cottony exudate was present on the tonsil, and in the following two days it had spread to involve the soft palate and opposite tonsil. It was partly adherent to the underlying mucous membrane, and fragments were expectorated when the child coughed or gagged. Three days after the onset of the illness, after picking his nose, he developed a severe nose bleed which required packing. The child's throat condition was diagnosed then by an ambulance surgeon as acute tonsillitis. After five or six days, with temperature ranging between 102° and 103°F., the fever subsided. On the sixth day after the onset of the illness he suffered another epistaxis which again required packing of the nose. He was seen for the second time by another ambulance surgeon who said "the child's heart was affected and the liver was enlarged." Removal to a hospital was advised, but the mother refused. The next day the boy complained of abdominal pain and vomited green-colored material. It was noted at this time that his speech was nasal in character, and that fluid would pour from his nose if he drank too rapidly. Vomiting continued intermittently until the time of hospital admission. About two weeks after the onset of his illness he began to have dyspnea and edema of the face which gradually increased, and three days before admission edema of the feet was also noted. At about three o'clock on the morning of admission the child voided. Immediately following this he became very noisy, complaining of pain on the right side of his neck. He rapidly became unresponsive with open staring eyes and limp extremities. He recovered and was brought to the hospital where a similar incident occurred in the Reception Ward.

*Examination.* The child was pale, dyspneic and perspiring. There was no rash. The pharynx was reddened and the tonsils inflamed; a follicular exudate was noted on the left. There was a small palpable gland on the right side of the neck. Slight cyanosis of the finger nails and a suggestive puffiness of the subcutaneous tissues

was present. There was pitting edema over both tibiae. The lower ribs extended outwards because of abdominal distention, and the labored respirations caused the sternum to retract. The abdomen was relaxed and the liver could be felt extending to the umbilicus on the right and across to the midclavicular line at the left costal margin. The spleen was not palpable. The heart was enlarged to the left on percussion and the apical impulse was in the fifth interspace outside the mid-clavicular line. There were no murmurs and the sounds at the base were heard poorly. The blood pressure was 100 systolic and 88 diastolic. His pulse was weak and exceedingly rapid. On neurological examination, the neck and abdominal muscles appeared weak, and the uvula deviated to the right. The child spoke with a nasal quality to his voice.

*Laboratory Data.* The blood hemoglobin was 68 per cent with a red blood cell count of 3,150,000 per cu.mm. The white blood count was 11,800 per cu.mm. There was a normal differential count. The urine revealed occasional red blood cells, casts and four plus albumin. The Schick test was positive. Throat culture revealed the presence of Klebs-Loeffler bacilli which gave a positive virulence test. The electrocardiogram revealed a sinus tachycardia with a rate of 150 per minute. There were occasional ventricular premature contractions, a tendency to right ventricular preponderance, and low voltage QRS. The latter was W-shaped in Lead I. The initial positive deflection was absent in Lead 4. These changes indicated severe myocardial damage.

*Course.* Clinical diagnoses were made of post diphtheritic myocarditis with congestive heart failure, and post diphtheritic pharyngeal paralysis. On the morning after admission the child was given 20,000 units of diphtheria antitoxin intramuscularly. In order to improve the cardiac status he was given 25 per cent glucose intravenously. Despite all forms of supportive therapy, there was progressive increase in cardiac failure. The cyanosis and edema became more marked and he died three days after admission.

*Necropsy Findings.* The *larynx* showed no evidence of diphtheria. In the *lungs* there were many small infarcts, due to multiple pulmonary emboli. The *heart* was dilated in all its chambers, and the myocardium was pale and grayish. A few friable thrombi were found adherent to the right auricular wall. It was evident that this was the source of the multiple pulmonary embolization. The *spleen* showed no changes. On microscopic examination the cardiac lesion was shown to be a diffuse one. There was destruction of the muscle with considerable fibrous tissue replacement.

*Comment.* *Dr. Klemperer:* During the acute stage of diphtheria the spleen often shows lymph follicle hyperplasia with central necrosis. The action of the diphtheria toxin on the heart muscle has been followed in experimental animals. The heart muscle degenerates and this process may continue until there is complete destruction of individual muscle fibers with subsequent replacement fibrosis. There is no primary inflammation and so the process is more correctly designated as myocardosis.

*Dr. Bachr:* A large proportion of cases of diphtheritic myocardial damage go on to complete anatomical and functional recovery. Complete rest and avoidance of cardiac strain in these cases is important until healing is complete.

Because of the delay in calling a physician, and the fact that eventually only an ambulance physician was called to control the epistaxis, I sus-



pected that the child belonged to a family on work relief. This proved to be true; the father was found to be earning less than eighty dollars a month through work relief, hardly enough to provide a bare subsistence for the family. Experiences such as this demonstrate that people in the lower ranks of work relief require, and should be provided with, the same home medical and nursing service which is available to those on home relief. This death was due to lack of medical care at the time the child developed diphtheria. The ambulance surgeon who failed to recognize the true nature of the condition when called to stop a nasal hemorrhage, was an inexperienced physician in training who hurriedly and successfully treated the emergency. Without excusing his negligence, the essential responsibility for this neglect lies in the lack of adequate provision for home medical care of people in this low income group.

Reported by *Abner Kurtin, M.D.*

*Wednesday, December 7, 1938*

### **Lupus Erythematosus Disseminatus**

*(From the Medical Service of Dr. George Baehr)*

*History* (Adm. 427721; P.M. 10888). This thirty-two year old Jewish female was admitted to the hospital for the first time on August 8, 1938. Her family and past history were non-contributory. Nine years prior to her entrance to the hospital she noted a flat, reddened eruption on the bridge of the nose which extended in butterfly fashion over both cheeks. This eruption did not itch, and was not associated with fever or joint pains. She consulted a dermatologist who told her that she had "lupus." At that time she was treated with gold, and with this form of therapy the eruption regressed slowly and disappeared within a year. However, during the two succeeding summers there were recurrences involving the ear, scalp, and episternal notch. Some lesions also appeared upon the scalp, and with this some areas of alopecia appeared behind each ear. Gold treatment again succeeded in causing the disappearance of the lesions. The patient was then symptom-free until two years before her hospital admission. At that time migratory polyarthrititis involving the knee, elbow, ankle, and proximal interphalangeal joints was noted. This was associated with slight fever. One year later there was a reappearance of the skin eruption after the patient had carelessly exposed herself to the sun. The involvement at that time included lesions on the forehead, eyebrows, bridge of nose and scalp, where the previously noted alopecia became more extensive. Gold therapy was reinstituted and shortly afterwards mouth lesions appeared for the first time. For four months the patient felt generally unwell, and then developed an illness which was diagnosed as pneumonia. This was characterized by cough, a temperature range to 106°F., bilateral chest pain intensified by deep inspiration, and

the expectoration of small amounts of mucoid sputum. This illness lasted about five weeks, following which there was a gradual improvement. Four weeks before admission tender, purulent, crusted lesions appeared on the gums. These were diagnosed as "trench mouth" and treatment with hydrogen peroxide mouth washes and a local application of arspenamine in glycerine was instituted. Despite this the lesions spread throughout the mouth and involved the lips. In addition, feverishness, occasional arthralgias and night sweats were noted.

*Examination.* The patient was a well-developed, moderately undernourished, chronically and acutely ill white female with conspicuous skin lesions of the face. Fundal examination revealed scattered white exudates of moderate size and a bilateral acute conjunctivitis. The lips were markedly swollen and covered with ugly yellowish black hemorrhagic crusts, which surmounted diffusely reddened vesicular lesions which bled easily when brushed. There was similar involvement of the buccal mucosa and gingiva with a necrotizing gingivitis. There were firm, small, shotty cervical and axillary nodes. On chest examination, there were a few crackles heard on the right lower axilla. The heart was not enlarged and there was a short soft systolic murmur at the apex. The blood pressure was 125 systolic and 80 diastolic. The edge of the liver was palpable at the costal margin. Vaginal examination revealed a diffuse granular appearance of the mucous membrane, with many vesicular and bullous lesions covered by a copious discharge. The skin over the face showed a deep pigmentation in a butterfly distribution extending over both cheeks. Within this zone there were numerous small areas of brownish pigmentation and telangiectasis. Similar lesions were present on both auricular pinnae, over the manubrium of the sternum, the back of the neck and several over the scalp. The hair on the eyebrows was scanty and there were several areas of alopecia of the scalp.

*Laboratory Data.* The blood hemoglobin was 58 per cent with a red blood cell count of 3,500,000 per cu.mm. The white blood cell count was 4,900 per cu.mm. (polymorphonuclear neutrophils, 62 per cent segmented; 19 per cent non-segmented; lymphocytes, 15 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent; basophiles, 1 per cent). The platelets were 250,000 per cu.mm. The urine examination revealed a fixation of specific gravity from 1.010 to 1.012. Albuminuria varied from one plus to two plus and repeated microscopic examinations showed the presence of granular and hyaline casts, with occasional red blood cells and clumped white cells. The blood urea nitrogen on admission was 24 mg. per 100 cc.; the sugar was 85 mg. per 100 cc. The blood Kahn was negative while the blood Wassermann was anti-complimentary on two occasions. Staphylococcus aureus Alpha was cultured from the urine; two blood cultures were sterile. Sputum, throat and mouth bacteriological studies revealed no significant organisms. The electrocardiogram showed a sinus tachycardia and QRS waves of moderately low voltage, indicating poor functional condition of the myocardium.

*Course.* Diagnoses of acute disseminated lupus erythematosus and drug eruption were made. The patient's mouth lesions were treated vigorously with sodium perborate and hydrogen peroxide mouth washes, and irrigations of 2 per cent acriviolet. Under this regime there was a transient improvement; however, at the end of the first week in the hospital the patient's temperature rose to 103.6+°F. and thereafter ranged between 102° and 105°F. She complained of pain in the left chest and on examination many medium moist, crepitant râles were heard and dulness was elicited over the left lower lobe. Concomitantly, there was an exacerbation of the lesions

over the bridge of the nose and cheeks, and new ones appeared on the abdomen, chest, and back. The characteristic lesion of the eruption was an erythromacule; however, occasional small vesicles were seen. During the ensuing week there was progressive consolidation of the right and left lower lobes. The white count rose to 25,300 cells per cu.mm. (92 per cent polymorphonuclear cells) and the blood urea rose to 49 mg. per 100 cc. The patient's condition grew worse and preterminally a friction rub in the antero-lateral left chest and precordial friction rub were heard. The patient died three weeks after admission.

*Necropsy Findings.* There was evidence of a bilateral acute and chronic pleuritis. On the right the pleura was adherent to the diaphragm. There was a confluent bronchopneumonia in both lower lobes. The tracheobronchial lymph nodes were enlarged, secondary to the pneumonic process. The pericardium revealed an old organizing pericarditis over the right auricle. The heart valves were normal. The liver showed some fatty change. The spleen was not enlarged. The kidneys, grossly, were mottled on the convex surface with bluish red areas which were slightly depressed (early scar formation). Vascular lesions were demonstrated on microscopic examination in the uterus, ovary and pericardium, with these lesions seen most clearly in the kidney. There many glomeruli showed necrosis of portions of the tuft, resembling the glomerular changes in subacute bacterial endocarditis. Some afferent arterioles showed necrosis of the wall. The follicular arteries of the spleen showed a conspicuously thickened adventitia.

*Comment.* Dr. Klemperer: Grossly no significant changes were noted in the organs of this patient with lupus erythematosus. The microscopic findings were predominantly those of necrotizing arteritis of several organs. The arterial changes in the spleen were also characteristic. The glomerular lesions found in this case have often been encountered in association with the typical "wire loop" lesions of lupus erythematosus.

Dr. Bachr: This was a typical case of lupus erythematosus with the clinical picture of skin lesions, fever, leucopenia, renal involvement and synovial membrane disease. In this disease non-bacterial thrombi are found on the heart valves in less than half the cases, the "Libman-Sacks" variety of endocarditis. It was not found in this case, in spite of the fact that a systolic murmur was present at the apex. The murmur is therefore of no diagnostic significance in determining the presence or absence of endocarditis in cases of this disease. This case teaches again that the condition from which this woman died is not a primary endocarditis or a primary heart disease. It is a disease of the body as a whole in which vascular changes occur in the skin, kidneys and various organs and tissues of the body, both functional and anatomic. At times the endocardium becomes involved as part of this process. Usually the synovial and various serous membranes are affected. The diagnosis is made on the clinical picture, presented typically by this patient, not by any heart findings. An anti-complementary Wassermann reaction is usually present. Again this case illustrates the predominance of the disease in the female sex.

Reported by Abner Kurtin, M.D.



Wednesday, December 21, 1938

## Carcinoma of the Stomach with Extensive Pulmonary Lymphangitic Carcinosis

(From the Medical Service of Dr. B. S. Oppenheimer)

*History* (Adm. 431619; P.M. 10988). The patient, a thirty-five year old fur salesman, was admitted to the hospital for the first time on October 31, 1938. He was entirely well until two months before admission when he began to complain of coryza and cough. The cough continued up until the time of admission, and he raised a few ounces of white, non-odorous sputum daily. Shortly before admission he developed anorexia and experienced substernal discomfort occurring about two hours after eating, and relieved somewhat by food. Two weeks before admission he began to have night sweats, and he felt feverish. During this illness he lost ten pounds in weight.

*Examination.* He was an asthenic male with subicteric tinge of the sclerae. Resonance was impaired at both apices and at the right lung base, with numerous fine râles heard in these areas. The heart appeared normal and the blood pressure was 130 systolic and 70 diastolic. The abdomen presented voluntary rigidity. It was not tender and no masses could be felt. Large internal hemorrhoids were found. The finger nails were slightly clubbed and the nail-beds cyanotic. Percussion tenderness was elicited over both sacro-iliac joints.

*Laboratory Data.* The blood hemoglobin was 84 per cent (Sahli). The white blood cell count was 9,100 per cu.mm. with a normal differential count. The sedimentation rate was 58 minutes. The blood chemistry findings were as follows: cholesterol, 340 mg.; bilirubin, 1.6 mg.; urea, 14 mg.; and sugar, 90 mg. per 100 cc. The van den Bergh was delayed positive. A sputum culture revealed the presence of pneumococcus type 31. A blood culture was negative. A heterophile reaction and agglutination tests for typhoid, paratyphoid, abortus and melitensis were likewise negative. Rehfuess test meal showed high free and total acid, with blood in the fasting specimen only. The urine was negative except for a faint trace of bile. An X-ray examination of the chest showed exaggerated pulmonary markings and numerous submiliary nodules which were interpreted as a chronic interstitial inflammatory process.

*Course.* The history suggested the presence of an unresolved bronchopneumonia. However, the early clubbing, cyanosis, progressive icterus, orthopnea and dyspnea made this diagnosis untenable. The patient ran a febrile course and continued to expectorate small amounts of mucopurulent sputum. The dyspnea, orthopnea and icterus increased progressively, the icterus index finally reaching a maximum of 38 four weeks after admission. A lymphoblastoma was suspected, but biopsy of an axillary node revealed no significant changes. A galactose tolerance test was normal and this, together with a cholesterol ester partition of 310/105 mg. per 100 cc., indicated that the icterus was on an obstructive basis. The stools were persistently guaiac negative, delaying for some time the consideration of a primary gastro-intestinal neoplasm. However, since it was felt that the pulmonary picture was not inconsistent with carcinosis, in spite of the guaiac negative stools and the negative Rehfuess, a gastro-intestinal series was performed. This revealed a filling defect in the antrum suggestive of carcinoma. Radiotherapy was given to the chest in the hope of alleviating the extreme dyspnea. The patient's course was progressively downhill, however, and he succumbed on the twenty-seventh hospital day, three months following the onset of his complaints.



*Necropsy Findings.* In the antrum of the *stomach* there was a small ulcerated carcinoma with infiltrated edges. The serosa and regional *lymph nodes* were involved, and were responsible for pressure on the common bile duct with resultant obstructive jaundice. There was a remarkable diffuse lymphangitic carcinomatous dissemination of the *lungs*, with all the lymphatics surrounding vessels and bronchi filled by carcinoma cells. In some areas the alveoli were also filled with the neoplastic cells giving the picture of a "carcinomatous pneumonia." The right *heart* was hypertrophied. Metastases were also demonstrated in *bone marrow* and *liver*.

*Comment.* *Dr. Klemperer:* This type of early and extreme lymphatic spread of carcinoma is unusual. It occurs chiefly in young persons, most frequently in gastric carcinoma.

*Dr. Bachr:* I wish to call attention to the paper by Dr. Greenspan which emphasizes that the diagnosis of lymphangitic carcinoma of the lung should be suspected when a patient under forty years of age has marked dyspnea and cyanosis without conspicuous clinical evidences of heart or pulmonary disease.

*Dr. Hitzig:* The right heart hypertrophy is secondary to increase in tension in the lesser cardiac circuit. The increase in pulmonary resistance to the circulation is based on two factors, the first being mechanical compression of the capillaries by the carcinoma, and the second an increase in lung rigidity.

Reported by *Abner Kurtin, M.D.*

## CLINICAL NEUROPATHOLOGICAL CONFERENCE

*Monday, February 13, 1939*

JOSEPH H. GLOBUS, M.D., *presiding*

### *Case 4.*<sup>1</sup> Multiple (Perineural and Meningeal) Tumors of Brain and Spinal Cord

*(From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen)*

*History* (Adm. 421215; P.M. 10773). A woman, when first admitted to the hospital on August 23, 1935, was 51 years old. From childhood she had experienced bladder difficulties and as far back as she could remember she had been rather obese and her body had had an abundance of hair. At the age of 40 (1924) she had begun to have convulsive seizures. Each attack was ushered in by a five minute period during which ringing like that of church bells would be heard in her left ear. This was followed by the sound of running water. She would then lose consciousness for about fifteen minutes during which time generalized convulsions, at first tonic, then clonic, would set in. She would become pale, cyanotic, and incontinent. Foam would appear on her lips. For one hour following an attack she would be drowsy, confused, and would speak incoherently. Such episodes would take place three or four times a year. At the age of 46 (1930) the seizures became less frequent and three years later she would experience only the auditory aura and weakness but not convulsions. Between the ages of 48 and 49 the patient became aware of increasing deafness in the left ear.

One morning in January 1935, she was awakened by sharp pains in the back of her neck and shoulders, radiating down both arms but especially down the left. These pains recurred daily, increasing in severity. They would last about an hour and were aggravated by movements of the neck. Two months later (March 1935) the patient noticed that her left hand had become pale, weak and swollen and that it felt numb and cold. The weakness and numbness gradually extended toward her shoulder. On one occasion during this time she fell, sustaining an injury to her left lower back. Two months before admission (June 1935) she began to drag her left leg and found walking to be increasingly difficult because of progressive weakness in this leg.

<sup>1</sup> The first three cases presented at this conference appeared in the September-October issue of the JOURNAL.

*Examination.* The patient was obese and hirsute and of a pituitary habitus. A vaginal examination revealed uterine fibromyomata. Her blood pressure was 154 systolic and 90 diastolic.

*Neurological Status:* The left palpebral fissure was narrower than the right. The pupils were irregular and unequal, the left being smaller, but both reacted well to light and in accommodation. There was a fine nystagmus in the horizontal plane on extreme lateral gaze. The fundi were normal. Bone conduction was better than air conduction on the left and the Weber test was referred to the right. The left upper limb was weak and spastic. The left hand was swollen and there was flexion contracture of the fingers. The left lower extremity was also weak. The deep tendon reflexes were hyperactive on the left side. The Babinski sign was present on the left side and an equivocal plantar response was elicited on the right side. There was diminished sensitivity to pain and temperature up to D 5 on the right side, to D 3 on the left side, and over both upper limbs. The hypalgesia and thermohypesthesia were more marked on the right side and especially marked in the right forearm and hand. The sense of touch was diminished in the left upper extremity from the middle of the arm distally. Two point discrimination was diminished in the left hand. Vibration sense was absent in the left wrist and hand. The left hand showed also a loss of stereognostic and position sense.

*Laboratory Data.* The cerebrospinal fluid was clear and colorless and under an initial pressure of 190 mm. of water. The Queckenstedt test revealed a block. The fluid contained 14 red blood cells and 4 mononuclear cells per cu. mm. The total protein was 90 mg. per cent. Serological tests were negative. X-ray examination of the skull was reported as normal. Hearing and caloric tests disclosed total involvement of the eighth nerve on the left and loss of function of the vestibular branch on the right. Perimetry showed no changes. Urine and blood examinations, including the blood Wassermann test, were negative. An electrocardiogram showed a left ventricular preponderance suggestive of left ventricular hypertrophy.

*Course.* One week after the patient's admission to the hospital, the hypalgesia and thermohypesthesia had advanced to reach the level of C 4 and, though the impairment was equal on both sides of the trunk, it was, as before, most marked in the right upper limb. Several days later there was further extension of the sensory disturbance to the region of C 3. Multiplicity of expanding lesions in the central nervous system was suspected. Neurofibromatosis (von Recklinghausen's disease) was believed to exist with the most offending tumor high in the spinal cord at about C 3, with tumors probably affecting both eighth nerves, and with possible extension of one of these downwards into the foramen magnum. To rule out the presence of intracranial tumors, ventriculography was performed. This was reported as being negative except for a slight increase in the size of the left lateral ventricle.

A laminectomy was performed on August 15, 1935. A tumor 1.5 by 0.5 cm. was found under the arachnoid, attached to the left third cervical nerve. It exerted pressure on the ventral surface of the cord, reducing it to the thinness of a ribbon. The tumor was removed. A Queckenstedt test now revealed the absence of obstruction. Subsequent pathological study of the tumor showed it to be a Schwannoma. Following the operation a superficial infection developed in the wound and the patient ran a low-grade temperature. Then she gradually began to show a return of functions and her temperature became normal. At the time of her discharge, September 16, 1935, her left arm and leg had regained much strength, the sense of touch was normal, position as well as vibration sense was returning in the left hand; and the hypalgesia below C 3 was now patchy. However, the astereognosis in the left hand persisted and there was a finger-to-nose ataxia on the left side.

*Second Admission.* The patient was readmitted to the hospital on March 10, 1938, two years after the laminectomy. For the first twelve months after the opera-

tion she had improved to such an extent as to experience only a slight difficulty in elevating the left upper limb and a sense of constriction about the wrist and fingers of the left hand. At the end of this period (August 1936) she began to experience a sense of pressure about her head; the noises in the left ear and weakness in the left arm recurred. Occasionally she would have difficulty in controlling urination. On two occasions she experienced the aura of bells ringing and water running but no convulsions followed. Spells of weakness and nausea would occasionally take place. Six months before her readmission (October 1937) she began to experience intermittent sensations of stiffness in the lower back which radiated laterally into both groins. In the course of the next month she began to experience a "caving in of the knees" when walking. She had the subjective feeling that her legs, especially the right one, were tremendously enlarged, numb, and cold, although they were warm to her touch. She no longer could distinguish between hot and cold water with her feet and would not know their exact position. Her legs became steadily weaker and felt constricted. At times the leg muscles would twitch. Two months before admission (January 1938) incontinence of urine, occasionally of feces, set in.

*Examination.* The patient was now 53 years old. She was alert and showed no personality changes. The findings on general examination were similar to those on her first admission except for the presence of a few brown pigmented moles in the skin over the body, not noted in the previous status. The eye findings were also similar to those of the first admission except that the nystagmus on lateral gaze was rotary rather than horizontal. There was nerve deafness of the left ear. The tongue tended to deviate to the left on protrusion. There was tenderness over the tenth, eleventh, and twelfth thoracic spines. The left upper extremity was weak, performed skilled acts awkwardly, and pass-pointed to the left. All deep tendon reflexes were hyperactive, especially in the left upper and right lower limbs. The Babinski sign was obtained on both sides. Up to the level of D 8 there was diminished sensitivity to touch, pain, and temperature. Above this there was an inconstant area of hyperesthesia. Position sense was impaired in the lower extremities and vibration sense was absent.

*Laboratory Data.* The cerebrospinal fluid was clear and colorless with an initial pressure of 270 mm. of water. The Queckenstedt test showed the presence of a block. Total protein, 180 mg. per cent; chloride, 130 mg. per cent as sodium chloride; sugar, 75 mg. per cent; cells, 7 mononuclears per cu. mm.; Pandy, 2 plus. Blood sugar, 135 mg. per cent; urea nitrogen, 10 mg. per cent; cholesterol, 325 mg. per cent. Blood microscopy and urine examinations were negative.

Lipiodol x-ray studies of the lumbar region were made with the patient in a marked Trendelenberg position. These showed an obstruction at the level of the upper border of D 9. An x-ray examination of the skull showed an osteoma in the right frontal sinus.

*Course.* The diagnosis of neurofibromatosis of the central nervous system was again made. The patient's most marked disability indicated the presence of one tumor at the level of D 8, and eight days after her admission (March 18, 1938) a second laminectomy was performed. No tumor was visualized, although obstruction about 5 inches above and below the wound was detected when attempts were made to pass a catheter up and down the subarachnoid space. The laminectomy was extended upwards; no tumor was found and the obstruction was seen to have been due to old dural adhesions from the previous operation. These were broken up and the operation was terminated.

During the following few days the patient ran a low-grade temperature. A Queckenstedt test disclosed a rapid rise but a slow fall in pressure, indicative of the presence of a partial block. The cerebrospinal fluid was xanthoehromic. On the tenth day after operation, the sensory level was at D 10 and the lower limbs were



found to be paralyzed. The patient was incontinent of urine and an indwelling catheter was inserted. Superficial sensibility became impaired in the upper limbs. Two days later she suddenly became noisy, making unreasonable demands and expressing suspicions of the people about her. Flaccid paraplegia set in. She developed cystitis and a sacral decubitus ulcer. With her temperature rising, she declined rapidly and died on April 2, 1938, five weeks after operation.

*Necropsy Findings. Brain. Gross.* The inner surface of the dura was the seat of numerous tumors varying from 1 mm. to 4 mm. in diameter. On the right temporal lobe about 3 cm. caudal to the pole, there was a firm, light-brown mass situated in the superior temporal sulcus and measuring about  $2 \times 1\frac{1}{2}$  cm. and protruding about one-half a centimeter above the surface of the brain. It was well-demarcated superficially from the surrounding tissue but appeared to extend into the depths and to be firmly attached there.



FIG. 10 (Case 4). The ventral surface of the cerebellum with part of the brain stem, showing the tumor in the left cerebello-pontine angle and the small pearly-white tumors on the right side.

On sectioning the brain, this tumor could be traced backward to about the middle of the temporal lobe. As it was traced posteriorly, it became reduced in size. It was very hard to the touch, uniformly pearly-white in color, and readily enucleated.

Another firm light-brown mass was present in the left cerebello-pontine angle (fig. 10). It was firmly attached to the eighth nerve and measured about  $2\frac{1}{2} \times 2 \times 1\frac{1}{2}$  cm. and caused distortion of the inferior surface of the cerebellum and the left half of the brain stem. The cranial opening of the internal auditory meatus was enlarged to the diameter of about  $1\frac{1}{2}$  cm. A small tumor, pearly-white in color and about 3 mm. in diameter was found among the rootlets of the right accessory nerve.

*Spinal Cord.* At the level of D 9-D 10 on the right lateral aspect of the cord and extending around it to its anterior aspect there was a firm, whitish, extra-medullary mass about  $1\frac{1}{2}$  cm. in its longer diameter.

*Microscopic.* Sections of the cerebello-pontine angle tumor stained with hematoxylin-eosin showed a very cellular tumor with the elongated cells arranged in

streaming crisscrossing bands and showing palisading of the nuclei (fig. 11). The tumor was fairly vascular but in some areas this vascularity increased to present an angiomatous appearance (fig. 12). Scattered through the tumor tissue aggregates of large round and oval cells were encountered (fig. 13). These contained a small deeply-staining, eccentrically located nucleus and homogeneous staining cytoplasm. They did not stain for fat with Searlet Red.

FIG. 11

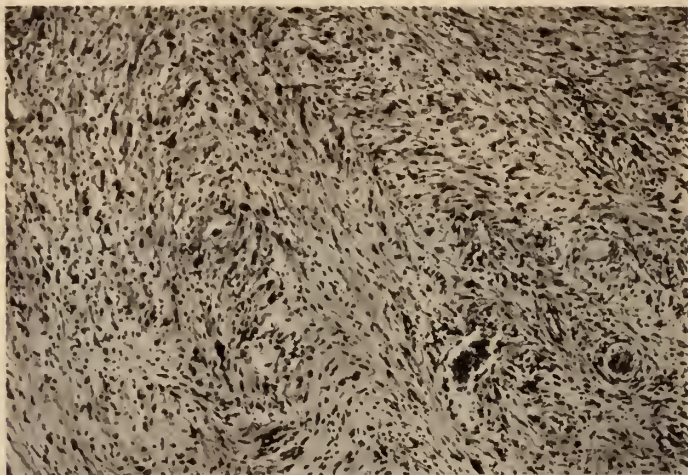


FIG. 12

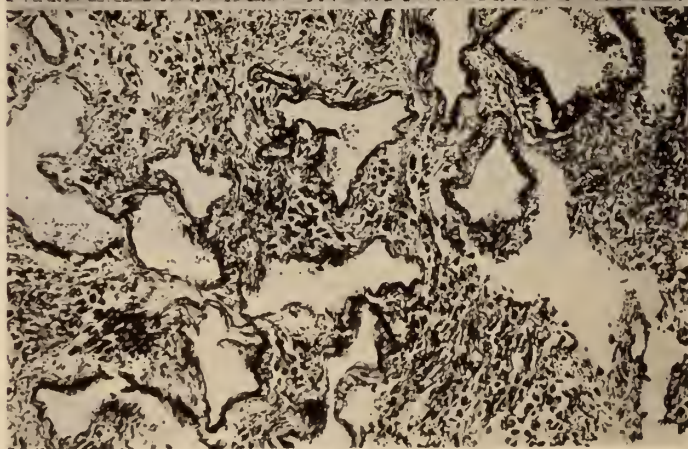


FIG. 11 (Case 4). Microscopic appearance of the tumor in the cerebello-pontine angle (Hematoxylin-eosin, 285  $\times$ ).

FIG. 12 (Case 4). An angiomatous area in the cerebello-pontine tumor (Silver stain, 90  $\times$ ).

Sections of the temporal lobe tumor, in addition to showing a neurinomatous character, presented in some areas accumulations of psammoma bodies and sheet-like masses of collagenous fibers (fig. 14).

The smaller tumors presented the cell arrangement and type of neurinomata.

A section of the spinal cord at the level of D 9-D 10 showed an area of gliosis in the lateral column apparently secondary to the pressure of the extra-medullary tumor.

*Comment* (Dr. Globus). Of particular interest in this case is the histological appearance of the angle tumor. It contained, in addition to features characteristic of neurofibroma (Schwannoma), blastomatous vessel

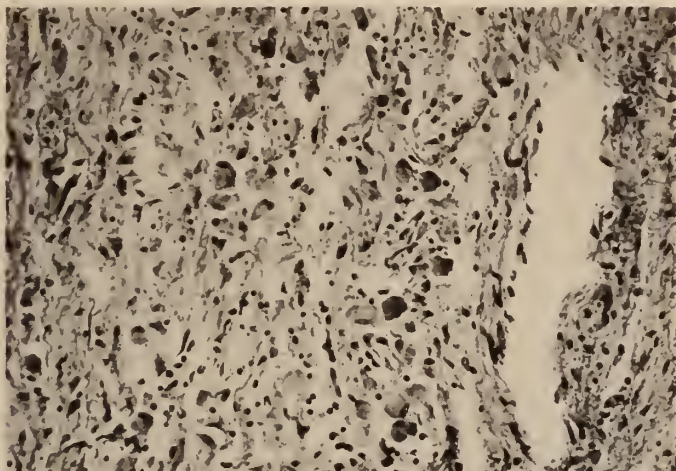


FIG. 13

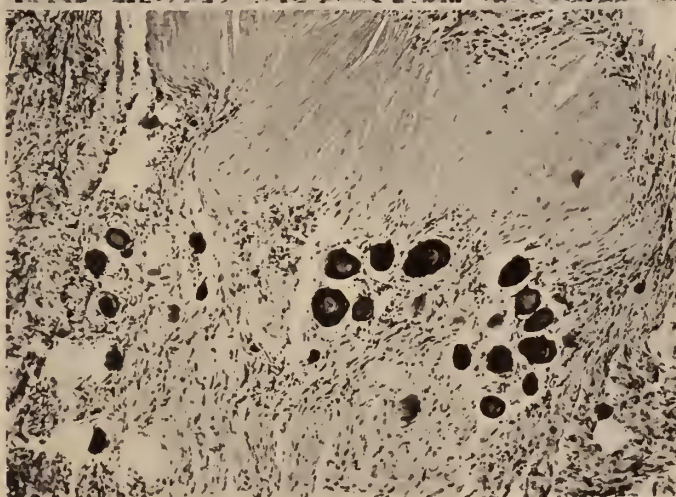


FIG. 14

FIG. 13 (Case 4). Large glial cells seen scattered through the tumor in the cerebello-pontine angle (Photomicrograph; Hematoxylin-eosin, 275  $\times$ ).

FIG. 14 (Case 4). Microscopic appearance of the tumor in the temporal lobe (Hematoxylin-eosin, 90  $\times$ ).

formations which in contradistinction to the former are mesodermal residues. The same admixture of mesodermal and ectodermal elements was noted in the "meningeomatous" tumor in the temporal lobe. It is, of course, not unusual to find a variety of tumors and tumor components,



of both mesodermal and ectodermal derivation, as an expression of von Recklinghausen's disease.

Reported by *D. Beres, M.D.*

*Case 5. Metastatic Carcinoma; bilateral, pontofacial*

*(From the Neurological Service of Dr. I. S. Wechsler)*

*History* (Adm. 398924; P.M. 10119). A man, 58 years of age, had experienced recurrent frontal and occipital headaches for many years. The headaches would occur weekly, would last a few hours, and were relieved by aspirin or black coffee. Occasionally they were associated with periods of dizziness. At the age of 52, while at work, the patient suddenly "collapsed" and remained dazed for several minutes. Four months before his admission to this hospital, his headaches became persistent and more severe. They would affect any region of the head and would be regularly accompanied by dizziness. Shortly thereafter he became irritable and complained of sharp intermittent pain in his chest and the upper part of his back, which was aggravated by deep inspirations. When examined at a New York clinic he was found to have marked scoliosis; an "aortic type of heart; old root branch fibrosis with central productive thickening; probable old scarring in upper lobes; and probable slight pleural thickening over apices, mainly left." One month before his admission to this hospital he again "collapsed." He was nauseated, vomited repeatedly, and suffered from severe headache which no longer yielded to medication. In the course of the following four weeks he lost eight pounds. On several occasions he was said to have had very dark stools. Walking became difficult and two weeks after his "collapse" he took to bed. On September 26, 1936 he was admitted to the hospital.

*Examination.* The patient was apathetic, pale, and emaciated. His skin was yellow. The trachea was deviated to the right. The dorsal vertebrae were tender to percussion. The cervical and inguinal lymph glands were enlarged. Both apices of the lungs were dull on percussion. The liver was slightly enlarged. The prostate gland was somewhat nodular. His blood pressure was 140 systolic and 105 diastolic.

*Neurological Status:* He walked unsteadily and tended to fall to the right. There was stiffness of the neck and a positive Brudzinski sign. His pupils were unequal, the left one being larger than the right, but reacted well to light and in accommodation. The fundi showed a moderate retinal arteriosclerosis. The left palpebral fissure was larger than the right. There was a left central facial weakness. The muscles of the extremities were wasted. The extended left arm tended to drift slightly from position. Rapid alternating movements were performed with a slight clumsiness on the left. There was a slight terminal unsteadiness on the left side during the finger-to-nose test. Finger movements were poorly performed on both sides. The deep reflexes were increased in the left upper extremity. In the lower extremities the right ankle jerk was greater than the left. The Babinski and Chaddock signs were present on the left side. The Lasegue and Patrick signs were present on both sides.



*Laboratory Data.* The cerebrospinal fluid: clear and colorless; total protein, 69 mg. per cent; Queckenstedt test, negative; Pandy test, one plus; cells, 3 per cu. mm. Roentgenograms of the chest disclosed old healed tuberculous lesions at both apices. X-ray examination of the spine showed a rarefaction and collapse of the fourth dorsal vertebra. X-ray examinations of the skull were reported as negative. An electrocardiogram was interpreted as indicating a poorly functioning cardiac muscle. Caloric tests gave normal vestibular responses. Wassermann tests of the cerebrospinal fluid and blood were reported as negative; the urine was also negative.

*Course.* A neoplasm in the right cerebral hemisphere was first considered, but the opinion was also expressed that the clinical picture was that of cerebral arteriosclerosis with a focal lesion in the right cerebral hemisphere. Headaches continued during the two days following admission; they were severe, did not abate with medication, and were occasionally accompanied by vomiting.

On the fourth day in the hospital papilledema appeared in the left eye. The roentgenological examination of the spine having been reported as showing rarefaction and collapse of the fourth dorsal vertebra, the diagnosis was made of multiple metastases from a primary lesion, probably in the gastro-intestinal tract. (The prostate when re-examined was excluded as the seat of a primary focus.) A gastro-intestinal examination was reported as showing an incomplete intestinal obstruction. The patient became progressively weaker. His papilledema continued to advance and hemorrhages appeared in the discs. Two weeks after admission a firm, irregular mass was observed in the abdomen just above the umbilicus. Ten days later another mass appeared in the right flank. The patient's condition continued to decline steadily and he died on November 3, 1936, five weeks after admission.

*Necropsy Findings. Brain. Gross.* The cerebral convolutions were somewhat flattened. On the ventral aspect of each cerebellar lobe there was a large, hard, but friable mass. Each mass was spherical in outline and, on its lateral surface, was adherent to the dura mater. The one on the left measured 3 cm. in diameter; the one on the right was somewhat larger. A small nodule was found adherent to the dura mater on the under surface of the tentorium.

Upon sectioning the brain, the ventricular system was found to be markedly dilated. In the cerebellum, the two tumor masses, described above, were found to be lodged in shallow depressions under the middle cerebellar peduncles (fig. 15).

*Tumor. Microscopic.* Sections of the tumor stained with hematoxylin and eosin showed masses of cells arranged in the form of glands (fig. 16). Two types of cells were present. One type, which lined the acini, was of fairly large size and contained a similarly large but pale nucleus at the base of the cell. The second type of cell was widely distributed throughout the supporting connective tissue. This was a small cell with a darkly-staining nucleus. Throughout the tissue there were masses of cells in various stages of necrosis. In some areas disintegration had advanced to the point where no cellular details could be discerned.

*General.* There was an annular carcinoma of the sigmoid causing partial obstruction. Metastases were present in the lungs and thoracic vertebrae. The right lung showed infected gangrenous infarcts and embolization of large branches of the pulmonary artery. There was bronchopneumonia and an organizing fibrinous pleuritis on both sides. In addition there were bilateral fibrous apical tuberculosis, nephrocirrhosis, atherosclerotic *lenta incipiens*, and a fibroadenoma of the prostate.

*Comment (Dr. Globus).* The symmetrically bilateral location of the tumors in a region close to the pontofacial angle, with the lesion being metastatic in character is rather unusual. This very symmetry of location and size would suggest that they took origin simultaneously from the

same metastatic cell group, floating, so to say, in the vascular stream common to the branches which conveyed the tumor cells to their destination.

FIG. 15



FIG. 16

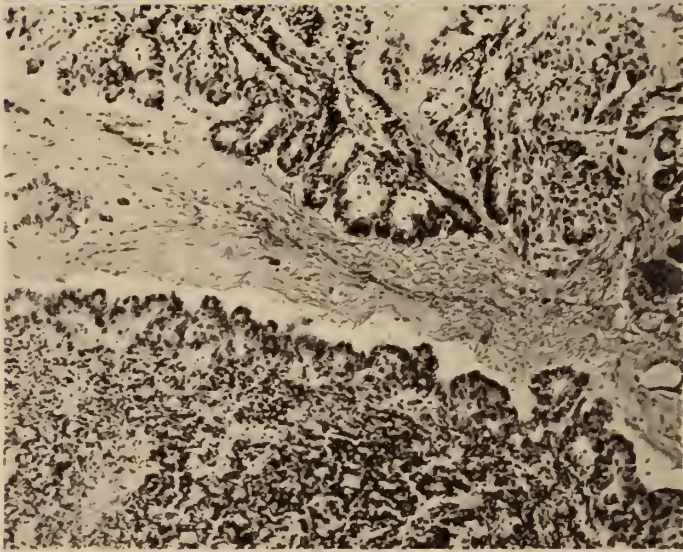


FIG. 15 (Case 5). Photograph showing two metastatic tumors lodged in the shallow depressions under the middle cerebellar peduncles.

FIG. 16 (Case 5). Microscopic appearance of the tumor in Figure 15 (Hematoxylin-eosin, 180  $\times$ ).

The clinical manifestation in this case, while suggestive of an intracranial neoplasm, offered almost no lead as to the probable location of

the lesion. It was unfortunate that there was no record as to otologic findings, for they could have given a clue as to the location of at least one of the lesions. The discovery of a metastatic focus in the spinal column, and the appearance of metastatic masses elsewhere, of course, pointed to the existence of metastases also in the brain. This fact, as well as the decline in the patient's condition, discouraged further efforts toward more accurate localization.

Reported by *T. Meltzer, M.D.*

*Case 6. Brain Abscess; multiple, bilateral, occipital*

*(From the Neurological Service of Dr. I. S. Wechsler)*

*History* (Adm. 413735; P.M. 10513). A painter, aged 38 years, was apparently well until six days before admission to the hospital when he began to experience persistent bitemporal headaches. The day following the onset of headache, impairment of vision set in; only light and shadows were recognized in either eye. He was moderate in the use of alcohol. He gave a history of a chancre in 1922, treated with twelve intravenous injections.

*Examination* (September 7, 1937). The patient was well-developed, well-nourished, and mentally clear. There was a horizontal nystagmus on right lateral gaze. He could perceive only light and shadows with either eye. The pupils were equal and reacted to light and in accommodation; the extra-ocular muscles were intact. The right knee jerk was more active than the left; the abdominal reflexes were absent on the right side.

*Laboratory Data.* Examinations of cerebrospinal fluid, blood, and urine were negative, except for a blood sugar of 285 mg. per cent and a leucocytosis of 15,700.

*Course.* The intact pupillary responses and the negative fundi suggested the probability that the pathological process causing the blindness had its location in the optic system somewhere caudal to the geniculate bodies. The ophthalmologists, however, could not dismiss the possibility of retrobulbar neuritis. The "meagre" focal signs and the absence of papilledema were thought to point against a brain abscess as a likely diagnosis.

On the third day in the hospital a sudden change took place in the condition of the patient, he became exceedingly pale, and his temperature began to rise. He was alternately restless, confused, semi-comatose, and delirious. He responded poorly to questions and pulled at the bed-clothing. Retraction of the head, neck rigidity, and positive bilateral Kernig signs appeared. Transient ankle clonus and equivocal Babinski responses were elicited bilaterally. A lumbar tap yielded yellowish cerebrospinal fluid with an initial pressure of 310 mm. of water. It contained 13,500 cells per cubic millimeter (80 per cent polymorphonuclear neutrophils). The Pandy test was four plus. The total protein was 360 mg. per cent. Cultures of a specimen of spinal fluid showed: no growth on the first four occasions, Gram-positive rods in the fifth culture, and anaerobic diphtheroids and anaerobic streptococci in the sixth culture. The seventh culture was negative. The diagnoses of purulent meningitis, and purulent meningo-encephalitis, secondary to empyema of the sphenoidal sinuses, were considered.



With the probability of an osteomyelitis of the sphenoid sinus in mind, a bilateral speno-ethmoidectomy was performed on September 9, with negative findings. It was then decided that involvement of the occipital lobes was the most probable cause of the blindness. The patient was treated with antimeningococcic serum intraspinally and prontosil intramuscularly and orally. There was no improvement; his temperature rose to 106°F., and he died on September 12, 1937.

*Necropsy Findings. Brain. Gross.* The meningeal blood vessels were engorged. Along many of the veins on the convex surface of the brain there were thin streaks of white exudate. Both occipital lobes contained extensive fluctuating areas, over which the brain tissue appeared thin and bluish. Perforations in these areas gave

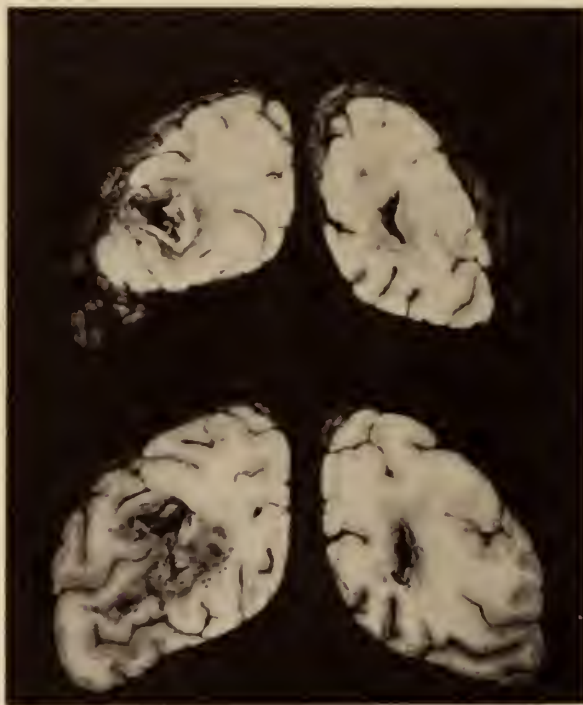


FIG. 17 (Case 6). Gross appearance of the abscesses in the occipital lobes.

rise to the escape of thick yellowish-green pus. Smears of this pus showed polymorphonuclear leucocytes and Gram-positive cocci in pairs and short chains.

On sectioning the brain, there was moderate enlargement of the ventricular system. The ependymal lining of the posterior horn of the left ventricle was covered by a purulent exudate. The choroid plexuses in both lateral ventricles were opaque. Several brain abscesses were found (fig. 17). One was multilocular and occupied the right occipital lobe extending posteriorly from about the end of the posterior horn of the lateral ventricle to within one centimeter of the occipital pole. Another, somewhat smaller and collapsed, presenting a better defined capsule, was found in the left occipital lobe on a level with the abscess in the right occipital lobe. It could be followed all the way to the tip of the left occipital pole increasing in size in its course backward. It was probably the somewhat older abscess; at any rate, it had a better organized wall, as compared with that on the right side.



*Microscopic.* The older brain abscess cavity (fig. 18) contained densely packed cellular debris, polymorphonuclear leucocytes, and mononuclear cells. A narrow zone containing relatively few nuclei marked the separation of the abscess wall from its contents, and was in turn surrounded by a wide, vascular, and highly cellular zone. Dense connective tissue fibers contributed to the organization of this layer. Some of the larger vessels in this region were enveloped by a perivascular lymphocytic infiltration. At the periphery of the vascularized zone the connective tissue increased in density to form a narrow but well-demarcated band, rich in blood vessels. This band could be traced to the pia arachnoid membrane of adjacent cerebral cortex.

A section of cerebral cortex taken at some distance from the abscess showed the pia arachnoid to be thickened and infiltrated by mononuclear cells and polymorphonuclear leucocytes. While the cerebral cortex showed no discernible changes, the

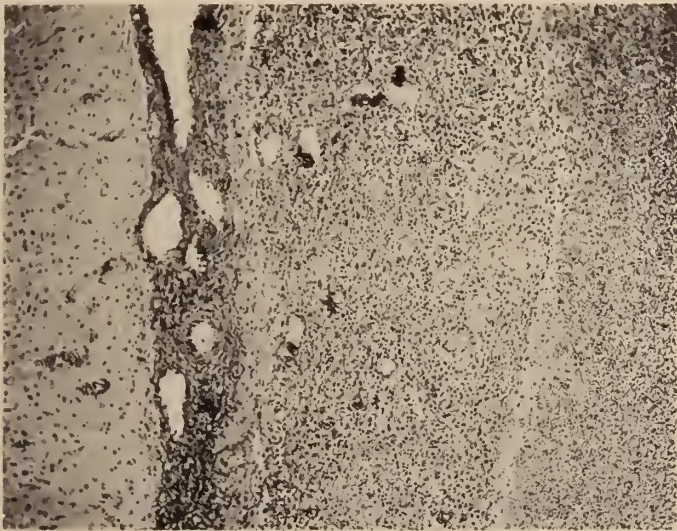


FIG. 18 (Case 6). Microscopic appearance of an abscess shown in Figure 17. Note the thickness of its wall and its proximity to the surface.

subeortex displayed a diffuse gliosis with quite marked glial mobilization about blood vessels.

A section of the brain with ependymal lining (in the region of the posterior horn of the lateral ventricle) showed purulent exudate adherent to the latter with exfoliation of ependyma in some areas. The subependymal blood vessels showed perivascular infiltrations.

*General.* The findings included rheumatic heart disease; patent foramen ovale; purulent bronchitis; acute congestion of the lungs and liver; acute infectious splenitis; right indirect inguinal hernia (omental); and cholesterosis of the gall bladder.

*Comment* (Dr. Globus). The location of the lesion fully explains the blindness in the presence of normal pupillary reactions, since the oculomotor nerves and the primary visual arc from the retina to the geniculate bodies were left intact. However, there is still a marked discord between the rather short clinical history and the chronicity of the brain abscesses.

Reported by *H. E. Yaskin, M.D.*

## ABSTRACTS

AUTHORS' ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Mitral Stenosis, A Correlation of Electrocardiographic and Pathologic Observations.*

K. BERLINER AND A. M. MASTER. Arch. Int. Med. 61: 39, January 1938.

One hundred and thirteen fatal cases of rheumatic disease of the mitral valve, with autopsy records, were collected and their electrocardiograms analyzed. The presence of associated lesions of other valves was found to be the most important single factor affecting the electrocardiograms.

Notching of the P wave was found to be the principal electrocardiographic sign of mitral stenosis. Marked increase in height and width of the P wave, however, was found to be common only in cases of mitral stenosis associated with disease of the tricuspid valve, and, in these cases, the notching was generally more marked.

The two principal factors which determined ventricular preponderance were the tightness of the stenosis, and the presence of other associated valvular lesions. Right ventricular preponderance was not found to be a characteristic sign of uncomplicated mitral stenosis. It was generally found in the "button hole" type of mitral stenosis, but still more frequently was caused by an associated lesion of the tricuspid valve.

A correlation of post mortem observations and electrocardiograms revealed that the electrocardiographic signs of ventricular preponderance, when present, indicated the anatomical relationship of the ventricles correctly in 89 per cent of the cases.

*Right-Sided (Regional) Colitis.* B. B. CROHN AND A. A. BERG. J. A. M. A. 110: 32, January 1, 1938.

The authors recognized the fact that approximately 20 per cent of the cases of colitis are of the regional or segmental type. The right side of the colon is favored in this localized form, in contrast to the left side of the colon, which is the point of origin of the universal form. Segmental colitis usually begins in the ascending colon or near the hepatic flexure, spreading in the course of years downwards, gradually encroaching upon the remaining or distal colon; it also spreads proximally to involve the distal ileum.

Surgical resection offers a radical and permanent cure. When performed in two or three stages, the mortality is low, the end results most satisfactory. No permanent ileostomy or colostomy is countenanced.

*Ulcer Recurrences Attributed to Upper Respiratory Tract Infection.* B. B. CROHN AND G. SHWARTZMAN. Am. J. Dig. Dis. & Nutrition 4: 705, January 1938.

An unusually severe and widespread grippe epidemic was followed by an exceptionally large number of peptic ulcer cases with gross hemorrhage. This occurrence

corroborated a fact known, but insufficiently stressed, namely, that upper respiratory infections lead to ulcer recurrences. The mechanism invoked is probably that of the Shwartzman phenomenon, a bacterial non-specific activation in the respiratory passages acting distally to cause local necrosis in the base of a peptic ulcer.

*The So-Called Hepato-Renal Syndrome.* J. H. GARLOCK AND S. H. KLEIN. *Ann. Surg.* 107: 82, January 1938.

The various clinical and pathologic aspects of the so-called "hepato-renal" syndrome occurring after operations upon the gall bladder and biliary ducts, as reported in the literature, are considered and discussed. Many of these reports are found to be wanting in post mortem studies. Those that include necropsy examinations present a curious lack of uniformity of the pathologic picture, which raises the question why one case presents minimal findings at autopsy, while another, with the identical clinical picture, may exhibit extensive hepatic and renal degenerative changes.

A possible explanation for this considerable variation in degree and extent of the pathologic findings is suggested. It seems possible that many of these patients have some degree of kidney damage before the surgical attack on the biliary system, with a small margin of safety from the standpoint of renal reserve. This impairment may not be apparent or demonstrable by any known laboratory methods. Following the operation upon the diseased biliary tract, with its associated surgical trauma and the greatly altered physiology that must necessarily follow, the already impaired kidneys are unable to cope with the additional load thrown upon them and soon break down completely. The clinical picture, with the relatively free interval of five to ten days after operation, is suggestive confirmation of this thought.

A case is reported in detail in which, five days after operation for calculus gall bladder and bile duct disease, there ensued a clinical course characterized by progressive asthenia and uremia with terminal icterus. Death occurred on the thirteenth postoperative day. The post mortem findings, contrary to the severe liver and kidney changes reported in the literature, consisted only of mild parenchymatous degeneration in these organs, and acute and chronic cholangitis. These changes certainly could not be held responsible for the clinical course of the patient. The kidneys, however, showed some focal interstitial inflammation manifested by nests of lymphocytes, plasma cells, and infrequent polymorphonuclear leukocytes within the stroma of the medulla. In addition, there was a striking glomerular lesion. This consisted of an increase in the size of the glomeruli, which was due to prominence of the intercapillary connective tissue framework which appeared spongy, as if distended by fluid. There was no increase in the cellularity of the Malpighian corpuscles. This glomerular picture bears a strong resemblance to the acute intercapillary glomerulonephritis described by MacCallum and considered by him to constitute the initial stage of the chronic condition known to clinicians as glomerulonephritis.

In conclusion, the authors have formed the opinion that no logical or satisfactory explanation of the so-called "hepato-renal" syndrome has as yet been offered. Although thought by many authors to follow surgery of the biliary tract only, the same syndrome has been known to follow operations upon the gastro-intestinal tract. Also, after extensive cutaneous burns, conditions known to be closely linked with disturbances of protein metabolism do occur.

*Theca Cell Tumors.* S. H. GEIST AND J. A. GAINES. *Am. J. Obst. & Gynec.* 35: 39, January 1938.

The anatomic and histologic characteristics of theca cell tumors of the ovary are described, together with their distinctive clinical and hormonal features. Though the feminizing changes produced are similar to those associated with granulosa cell



tumors, these neoplasms are identified as a separate entity. Histogenetically they are related to the theca interna cells of the ovary or their precursors.

Descriptions are given of six cases illustrating variations from the more benign fibroma type to the highly cellular and malignant type. A correlation is made between the presence of hormonal changes and the presence of intracellular, doubly refractile fat containing cholesterol and cholesterol esters. It is suggested that some of the ovarian neoplasms previously diagnosed as fibromas, fibrosarcomas or granulosa cell tumors may, in the light of this investigation, prove to be of theca cell origin.

*Vitamin D and Myopia.* J. LAVAL. Arch. Ophth. 19: 47, January 1938.

A review of the various theories advanced for the etiology of myopia is given. The histology of the cornea and sclera is discussed and also the changes which occur in these tissues when there is vitamin D avitaminosis and calcium deficiency. The relationship between pregnancy and myopia, the association of blue scleras with brittle bones, and the increase of myopia during adolescence, all these are considered.

A description follows of the clinical results of the use of vitamin D and calcium in the form of viosterol and milk on forty-eight myopic patients over a period of six years. It is concluded from the data that vitamin D does not reduce the amount of myopia; it does not keep it stationary, nor does it prevent as rapid an increase as is usually found in patients who have not used vitamin D and calcium.

*Disease of the Spinal Cord in Pregnancy.* W. NEEDLES AND C. DAVISON. Am. J. Obst. & Gynec., 35: 52, January 1938.

The authors report two cases of myelopathy of pregnancy; one studied clinicopathologically and the other, clinically. On the basis of their findings they conclude that the most likely explanation for the condition is a toxic process. The possibility of a deficiency in vitamins is not, however, ruled out.

*The Nature of Glomerulonephritis.* GEORGE BAHR. Bull. N. Y. Acad. Med., second series, 14: 53-64, February 1938.

It has become necessary to redefine glomerulonephritis, for old misconceptions have been revived in several recent pathological and clinical publications so that the subject is again in danger of being enveloped in the confusion which existed up to twenty-five years ago. The fault lies with some of our pathologists who lay undue weight upon cellular morphology and too little upon the whole picture of the disease. They exaggerate the significance of non-specific cellular changes commonly seen post mortem in some of the renal glomeruli and regard them as lesser degrees of glomerulonephritis. This misinterpretation of a common post mortem finding is analogous to the clinical error of diagnosing glomerulonephritis merely because of the presence of albumin and casts or of red blood cells in the urine.

It is the purpose of this paper to review some clinical and pathological experiences which demonstrate: (1) that acute glomerulonephritis (acute Bright's disease) is a sharply circumscribed entity; (2) that it is part of a disease of the body as a whole; (3) that its clinical manifestations can be related to characteristic pathological phenomena in various parts of the body; (4) that the disease has a specific etiology and pathogenesis.

Evidence is presented which demonstrates that acute Bright's disease cannot be due to the direct damaging effect of streptococci or their toxins upon the kidney. Nor can it be caused by the mere killing off of streptococci, for this must be taking place constantly in patients with prolonged streptococcemias. The sudden explosive occurrence of acute diffuse glomerulonephritis is a specific reaction, concerned in some still unknown manner with the mechanism of recovery from streptococcal infections.



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Manuscripts, abstracts of articles, and correspondence relating to the editorial management should be sent to Dr. Joseph H. Globus, Editor of the Journal of The Mount Sinai Hospital, 1 East 100th Street, New York City.

Changes of address must be received at least two weeks prior to the date of issue, and should be addressed to the Journal of The Mount Sinai Hospital, Mt. Royal and Guilford Avenues, Baltimore, Maryland, or 1 East 100th Street, New York City.

## THE FIRST NEUROLOGICAL DIVISION IN NEW YORK CITY— AT THE MOUNT SINAI HOSPITAL

BERNARD SACHS, M.D.

My years of service at The Mount Sinai Hospital have meant so much to me that I yielded to the Editor's repeated bidding to tell of the rôle this Hospital played in the development of Neurology in this City.

I am going to tell the story and if my own person is too much in evidence (*Quorum pars magna fui*), sorry, but facts are facts. In the late Seventies and early Eighties of the last century, Neurology had already made a distinct impression on medical science here and abroad. Charcot, Hughlings Jackson, Erb, Weir Mitchell, William Hammond, Seguin, Spitzka and Starr had made fundamental contributions to this rapidly developing specialty, but General Medicine, as it does to this day, tried to hold its child in check and to deny its rights. No private (voluntary) hospital had established wards for nervous diseases. The General Medical Attending was supposed to know it all. Discussing this question with Abraham Jacobi as far back as 1885, I asked him whether he realized that a knowledge of Neurology has to be acquired and does not come by intuition. He pardoned my boldness and in spite of this frontal attack, we were good friends many years thereafter.<sup>1</sup>

My first dispensary work (1884) was done as a Volunteer Assistant in the Surgical Division, under Arpad G. Gerster, in the old German Dispensary at Second Avenue and Eighth Street. I doubt whether Gerster thought highly of my surgical ability, but it helped to make me known to him and he became interested in what I was doing. He was fully alive to the important questions of cerebral localization and after a year or two invited me to advise him in the old Lexington Avenue building of The Mount Sinai Hospital regarding cases of epilepsy and brain tumor. It was Gerster's appreciation of neurological science that was largely responsible for my appointment as "Consulting Neurologist" to The Mount Sinai Hospital in 1893. For many years there was the friendliest sort of coöperation between Gerster and myself at the Hospital and at the Polyclinic where both of us were active. Conjointly we published articles on the Surgical Treatment of Epilepsy in the *American Journal of Medical Sciences* in 1892 and 1896; also an article in the *Deutsche Medizinische Wochenschrift*, 1896 (good old days!). In the latter article we re-

<sup>1</sup> I was particularly proud that I succeeded him in the Presidency of the Medical Board and that both of us had been President of the New York Academy of Medicine.

ported a critical analysis of the result in nineteen cases—a significant series in those pioneer days, and as I reread the conclusions they may even, at this day, stand “approved as read.”

This association with Gerster made my consulting work of great interest to me and, I believe, of special service to the Hospital. Although I had been made Professor at the Polyclinic in 1888, four years after I entered practice, and had clinical opportunities at the Polyclinic with Gerster, Wyeth, and Landon Carter Gray, and at the Montefiore Home with Dana, Harlow Brooks, Fraenkel and others, and I should have been flattered by the President's report (1893) (in which he stated that “Dr. S. Lustgarten had been appointed Consulting Dermatologist and Dr. B. Sachs Consulting Neurologist, two new positions created this year”); that “no separate wards or beds are assigned for these departments the object being mainly to afford consultation with these *eminent* specialists for the benefit of certain classes of patients in the Hospital”), yet I was not happy and soon felt, what I have said in later years, somewhat facetiously, that in a hospital a “consulting” physician is a physician who is never consulted. I was willing to be demoted to Attending Neurologist, if special wards would be assigned to me. Here again, Gerster and several good friends among the Directors were of help to me; and finally in 1900, the Neurological Service (for years never more than six male and six female patients) was created at The Mount Sinai Hospital; and the first special Neurological wards in any of the larger private hospitals of New York City were established. I must add, in justice to my colleagues on the Medical Board, that even as Consulting, I was made a member of the Board and almost immediately made a member of the Board of Examiners, together with Janeway and Arpad Gerster. I tried to be fair to the applicants, but some soon discovered that I gave preference to the candidate who could write prescriptions proving that he had an inkling of Latin forms and terms.

In those days, Janeway, Rudisch, Alfred Meyer, Heineman were the Attending Physicians; Gerster, Wyeth, Stimson and Fluhner were the Attending Surgeons; Paul F. Mundé was Gynecologist (preceding my friends Joseph Brettauer and H. N. Vineberg); Gruening was Ophthalmologist and Aural Surgeon. He was followed several years later by Charles H. May and Carl Koller. Nathan Brill and Manges were appointed Attending Physicians, while Koplik was appointed Attending to the Children's Service. It may recall still more vividly that time “long ago” if I state that Howard Lilienthal had just appeared on the horizon, having been appointed Assistant Attending Surgeon in 1895 and raised to the rank of Attending Surgeon in 1899; A. A. Berg and C. A. Elsberg were Adjunct Attending Surgeons; Edwin Beer, having graduated from the House Staff in 1902, was far from the top. All of them have since “arrived,” and, to my sincere regret, some have passed to the great beyond.



I have happy recollections of the Medical Board meetings with Janeway and Gruening, the latter acting as Secretary to the Board, and of the occasional visits from the President, Mr. Isaac Wallach and, later on, and for many years, of visits from Mr. George Blumenthal.

Once I was on a par with other Attending Physicians and Surgeons, I had smooth sailing. Even Jacobi allowed that Neurology deserved to be on the map and all the others referred cases freely to the Neurological Service.

While I had been enabled to utilize the splendid material of the Polyclinic, with which I had been connected since 1886, and of the Hospital for Ruptured and Crippled (through the courtesy of Gibney), it was a welcome enlargement of my field of activity to have a special service in which neurological cases could be examined most carefully, employing and testing always the newest diagnostic and therapeutic methods. I felt that the chief aims of such a service should be the considerate treatment of the patient, making use of the most recent methods, the training of an adequate House Staff and, above all, the development of a group of able associates and assistants who would be certain in the course of time to contribute materially to the advance of neurological science. Incidentally, I stressed the importance of the doctor looking neat, being scrupulously clean, using good English, and articulating distinctly. I feel that I may claim to have succeeded in these various aims and am certain that I gave the staff every opportunity for independent research and publication.

While I was deeply interested in new procedures and laboratory methods, the guiding principle was that bedside observation was of the greatest importance—that the diagnosis should be made at the bedside—that laboratory methods might be considered supplemental and corrective, but must not and cannot displace clinical observations based upon anatomical and physiological knowledge of the organs involved.

Whenever special medical or surgical knowledge was required, we called in special authorities in the Hospital. Another principle adhered to from the beginning was the encouragement given the House Staff and the Assistants to study each case independently, to present the report on official rounds, and receive either credit or well-meant criticism in the presence of the Staff and some visitors.

From the fact that some of my former staff have commented upon the advantage to them of my methods, I may feel that the service was a success. Parenthetically, I may add that one reason why I was specially concerned with the opportunities given my associates and assistants was that in my earliest years I was made unhappy while I was associated with a physician who never got away from the idea that the younger man knew nothing and that he knew it all. I cannot mention all the former assistants and associates who were subject to my tyrannous treatment,

but the general calibre is indicated by names well-known at this day: William Hirsch and I. Abrahamson in 1904; a little later Strauss, Friedman, Grossman, Keschner, and Wechsler. Globus was added to the group, and his neuropathological laboratory has added greatly to the value of the work done in the Neurological Division. Many others were active in the Dispensary. If there was any fault at the time, it was that the Out-patient Department Service was not intimately linked with the Hospital, although all the men were privileged to make rounds three times a week (9-11 a.m.) with the "Chief" and his aspiring Adjuncts and Assistants. Goodhart, Hausman and others were regular in attendance.

The Service was active from 1904 (in the present Hospital) until 1924, when I was retired because of age, and no doubt properly so.<sup>2</sup> The Ward facilities had been enlarged in 1922, when we moved into the present wards which had been established by my two brothers, Samuel and Harry Sachs, and dedicated to the memory of our parents.

Let me refer to some of the special work done in the Clinic. The first considerable epidemic of poliomyelitis was carefully studied; a few years later epidemic encephalitis had our closest attention. At all times we maintained a critical attitude in order to ascertain the exact truth and not fall victim to passing fancies. Syphilis of the nervous system had our special interest. It was the period of the Salvarsan therapy and of the Swift-Ellis treatment. We maintained our critical attitude; did not favor the general use of the latter and, as has been shown since, were correct in our conclusions. Just so in our years of study of the Wassermann reactions of blood and cerebrospinal fluid, we made very liberal use of the tests, but claimed that there were other equally important indications of constitutional syphilis and that a negative Wassermann did not exclude syphilis, especially if the pupillary reflexes—or the absence of them—indicated previous specific infection. In this work, Doctor Kaliski, who made rounds regularly with us, was very helpful. One of my former assistants reminded me only a short time ago of the repeated question I put to Kaliski—"Are the Wassermans all positive or all negative this week?"—showing that we were not completely overawed by these tests, much as we esteemed them. I hold it to be one of the chief functions of such a Hospital service to become acquainted with all newer methods of diagnosis and treatment, and to exercise sound critical judgment in evaluating and applying them.

During these years, the Service provided ample opportunities for studies on acute infectious myelitis, on tumors of the brain and of the spinal cord—wherein we had the support of the Neurosurgical Division and especially of Elsberg, A. A. Berg, and later on of Ira Cohen—on various forms of

<sup>2</sup>Although I have had some of the most active years in professional work since 1924.

paralysis agitans, notably after the study of epidemic encephalitis, on the muscular dystrophies, on erythromelalgia, scleroderma and other rare vasomotor conditions. This Service was, for a long time, the only one in the City to provide bedside observation of acute neurological diseases. At the Montefiore Hospital, chronic cases were studied carefully, but the Neurological Institute had not yet been established and Bellevue had not yet opened special neurological wards. It is a great personal satisfaction to me to know that the Neurological Division became, and has remained, an integral part of a great Hospital. I acknowledge the good work done by my successor, Strauss, and now by Wechsler.

I feel that with great opportunities come great obligations and I trust that in the impending development, especially of the newer electrical and electroencephalographic methods, and also in view of the recent advances in the chemistry of the brain, and of the impending era of chemotherapy, the Mount Sinai Neurological Division will occupy a prominent rank. I also hope that in order to do full justice to the study of the neuroses and the neuropsychoses and to study them critically without being victimized by any one school of thought, this Service may be developed into a Neuropsychiatric Service, in which organic neurology will always play the important and fundamental rôle which it holds by right in the latter day development of neurology and psychiatry.

## THE PROBLEM OF OVARIAN FUNCTION AND MENSTRUATION<sup>1</sup>

BERNARD ZONDEK, M.D.

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In this lecture I am going to speak about some clinical and experimental investigations on the problem of ovarian function in menstruation. The largest part of this work was done in Jerusalem.

The knowledge of internal secretion (hormone research) has achieved immense progress during the last decades. This is particularly true of the sexual organs. Even at the beginning of the century little was known of the nature of the sexual functions. Anatomical research elucidated the interrelationship between ovary and uterine mucosa. Only after this did biological and chemical research begin and this led to the present advances. The first epoch of this research took place, in the main, in Europe; the second in America. I need not mention the names of those American workers who deserve our greatest gratitude for the elucidation of these problems. They are sufficiently known to all of you.

The cyclic changes occurring in the female organism are made evident by the monthly uterine flow. It is easily understood that since ancient times medicine has devoted much thought to this mysterious problem, and that the most varied explanations have been offered, according to the more or less advanced stage which medical research reached during each particular epoch. It was generally accepted in popular belief, as well as in ancient medicine, that the uterus was an organ of excretion, removing from the organism the harmful products of metabolism. Menstruation was, therefore, looked upon as a cleansing process of the utmost importance to the female organism.

*The ovum and ovarian function.* During the first decades of this century it was generally accepted (theory of Robert Meyer) that the ovum represented the center of the generative function, and that the entire process was governed by it. This theory of the primary importance of the ovum served as the basis of the theory of menstruation. If the ovum is not fertilized and, consequently, degenerates, the uterine mucosa, previously developed to receive the impregnated ovum, breaks down and is discharged. This phenomenon is accompanied by bleeding, which represents menstruation. Menstruation, therefore, was believed to represent

<sup>1</sup> Delivered in the Blumenthal Auditorium, The Mount Sinai Hospital, December 5, 1939.



the abortion of the unfertilized ovum. This theory of the primary importance of the ovum became no longer acceptable in 1925 when implantation experiments demonstrated that the anterior pituitary gland liberated an active gonadotropic principle. These experiments were performed simultaneously by P. E. Smith and myself, each of us working independently. With the help of the gonadotropic factor, it was possible to reproduce the entire generative process experimentally. The anterior pituitary gland, so I concluded, was the "motor" of the sexual function, and the gonadotropic hormones the superior general (unspecific) sex hormones. The follicle ripening hormone, Prolan A, produced in the anterior pituitary gland, initiates the production of folliculin in the ovary and the luteinizing hormone, Prolan B, produced in the anterior pituitary gland, initiates the formation of the corpus luteum and indirectly the production of progesterone. What is the significance of the ripening ovum within this cycle? That the production of folliculin, that is to say, follicular hormone, takes place independently of the ovum was demonstrated some years ago and is generally accepted today. Since after follicular rupture, corpus luteum formation sets in, without which true menstruation is impossible, it is obvious that the ovum is responsible for the entire second phase. Is it the ripening ovum which initiates the stimulus for corpus luteum formation? Our investigations, which we shall describe, show that this question must be answered negatively.

If gonadotropic hormone is injected into a hibernating bat, the follicle ruptures and corpus luteum formation takes place. Since in the uterus of the bat spermatozoa are also present, fertilization may take place. Thus it is possible to produce pregnancy in the bat in the middle of winter. If large amounts of prolan from pregnancy urine, or anterior pituitary hormone, are injected, a number of corpora lutea are formed, the ova, however, degenerating. Nevertheless, these corpora lutea function. The presence of an ovum is, therefore, no prerequisite for corpus luteum formation.

The objection can be raised that even if the ovum degenerates, it had, previous to this, produced a hormone which, in turn, stimulated corpus luteum formation. Therefore, it is necessary to provide direct proof for the fact that corpus luteum formation takes place, even if the ovum has been removed from the follicle. Such experiments were conducted by Westmann and myself in 1934. At that time I worked in Stockholm.

In the mature rabbit there are always follicles which are ready for rupture, but at no time are there corpora lutea. Follicular rupture and corpus luteum formation are initiated exclusively by copulation. It can be demonstrated that a follicle which contains no ovum may be converted into a corpus luteum in the same way as a follicle which contains an ovum. I removed an ovum from a follicle which was just ready to rupture, by aspiration, and resected the ovarian tissue in such a manner that only

this one empty follicle remained. Then gonadotropic hormone was injected into the animal. The follicle developed into a corpus luteum which produced progesterone. This could be definitely deduced from the decided transformation of the mucous membrane. The puncturing of the follicle itself has no effect on corpus luteum formation. With reference to the follicle it is, therefore, absolutely irrelevant whether or not the ovum is present.

*Ovulation and corpus luteum formation.* Up to this time, we believed that the formation of a corpus luteum in human beings presupposed that ovulation had taken place. But our experiments show that corpus luteum formation in the rabbit can be obtained without ovulation. Therefore, when progestational endometrium is procured by biopsy in women, we should say that only a corpus luteum has been formed and not that ovulation has necessarily occurred. While we are of the opinion that in general corpus luteum formation follows ovulation, there is also the possibility that a corpus luteum may be formed without ovulation.

Our experiments definitely prove that the theory of the regulating action of the ripening ovum can no longer be entertained. The ovum has its own life. It does not depend either on the hormonal process of the ovary, nor even on the gonadotropic hormone of the anterior pituitary. This is also shown by the fact that O. Swezy and myself found, in the ovaries of hypophysectomized rats, newly formed germinative cells and active cell division.

In summarizing, I wish to state the following: The ovum is of no importance with reference to the hormonal regulation of ovarian function. Without the anterior pituitary, ripening of the follicle and follicular rupture are impossible. Without the action of the anterior pituitary the ovum would never meet the spermatozoon, in other words, it could never fulfill its function. The anterior pituitary, therefore, controls the ovarian hormones, as well as the ovum, but the ovum leads its own independent life. Its development, that is, its ripening, depends neither on the follicle with its hormones, nor even on the anterior pituitary lobe.

Within this system the ovum is superior to the ovarian hormones, the function of the latter being exclusively that of preparing the uterus to receive the impregnated ovum. The ovary, therefore, is at the same time host and servant of the ovum. Thus the ovum is independent and only needs the help of the anterior pituitary to open the door and to release it from the follicle.

Since the ovum is of no importance with reference to ovarian function, it cannot play any rôle in connection with the mechanism of menstruation. Maturation of the ovum and corpus luteum formation run a fairly similar course in all mammals. In most of them, however, the involution of the mucosa is not accompanied by bleeding. Bleeding is exclusively met with in the highly developed species, man and monkey.

What are the forces that produce the bleeding? Is it really only the breakdown of the uterine mucosa, a passive process, which causes this event? Or is this bleeding an active process for the purpose of uprooting and eventually expelling the mucous membrane? To begin with, it is necessary to more clearly define the term "menstruation." Not every uterine bleeding signifies menstruation. In the human, and even more so in the animal, uterine bleeding can be produced by inducing hyperaemia. This bleeding may take place even from an atrophic mucosa. Menstruation, however, means a bleeding which takes place from a transformed mucous membrane. In the first phase the mucosa is developed by means of folliculin. After follicular rupture, in the second phase, the mucous membrane is transformed into the secretory stage through progesterone. The glands enlarge and produce mucus and glycogen, thus providing the nest for the impregnated ovum.

Only bleeding from, and expulsion of, such a progestationally developed mucosa is true menstruation. The important investigations of the American authors Corner, Hartmann and Allen demonstrated that in the monkey the summer cycle runs without follicular rupture, although uterine hemorrhages from the proliferative mucous membrane occur regularly. This non-ovulatory bleeding must be called pseudomenstruation, in contrast to menstruation, which is bleeding occurring from the progestationally transformed mucosa. The investigations which were carried out on monkeys were of the utmost importance for human pathology, as Novak first demonstrated. We know that there are women in whom bleeding occurs from a proliferative mucosa. These women, have, therefore, a pseudomenstruation. In such women follicular rupture fails to occur. This fact is of great significance in the problem of sterility. In 100 sterile women whose uterine mucous membranes were examined before menstruation, ten per cent were found to be in the non-ovulatory phase. This percentage is the same as that found here by Rock, Bartlett and Matson. Sterility, in these cases, was attributed to this cause. The mechanism of bleeding may be the same whether from a proliferative or a progestational endometrium. Unfortunately, our modern women know too much about hormones and their tests, but fortunately they do not feel the difference between the bleeding of pseudomenstruation and menstruation.

*Glycopenia uteri.* During the second phase the activity of progesterone becomes apparent by anatomical transformation of the uterine glands. The glands become larger and wider, assume corkscrew shape, and produce glycogen. This substance is probably of great importance to the young fertilized ovum which is to be imbedded in the mucous membrane. Progesterone has a similar function in all mammals, namely anatomical transformation of the glands, but—and this is of the utmost importance—it is exclusively in monkeys and humans that considerable quantities of



glycogen are produced in these glands. Up to now, the investigators have been satisfied with qualitative tests for glycogen, that is specific histologic color reactions. Since the proportion of glycogen found in the individual glands and in the different portions of the mucosa varies greatly, we did not believe it sufficient to perform qualitative tests only. So we tested the mucous membrane quantitatively for its glycogen content, by analyzing the total material obtained by curettage, except for one small piece which was subjected to anatomical examination. The analysis<sup>2</sup> was done according to the microdetermination method of Pflueger. Experiments of this kind have as yet only been performed by van Dyke in monkeys. The quantity of glycogen is given in terms of grams per cent glucose. I conducted such investigations in sterile women in the various phases of the cycle and the results were as follows: up to the moment of follicular rupture the mucous membrane contains but little glycogen, 0.1 per cent. During the premenstrual stage the glycogen content gradually increases up to 0.6 per cent. In some cases the following interesting findings were obtained: the uterine mucosa was in perfect order as to anatomical development, the glands had the corkscrew shape, they produced mucus but no glycogen, or else only very insignificant amounts of glycogen. The values obtained were, on an average, only 0.1 per cent. Thus we had the following findings: the glands were in the ovulatory phase, the anatomical transformation of the mucosa was perfect, but the glycogen formation was insufficient, or altogether absent. As far as I know, such abnormalities have not been observed as yet. I am inclined to term this condition "glycopenia uteri". I am convinced that these facts are important in reference to sterility. In these cases the mucous membrane contains no glycogen. This probably gives rise to the abortion of the fertilized ovum, since the ovum does not find the necessary provisions for its nutrition. I have not yet published these findings, which are an attempt at the determination of the chemical function of the uterine mucosa.

*Gonadotropic hormone and menstruation.* Now I return to the question: what is it that initiates menstrual bleeding? The mechanism of menstruation has been most carefully studied during recent years, particularly by American authors. I shall only mention the papers of Edgar Allen, Corner, Engel, Robert T. Frank, Firor and Geiling, Hartmann, Hisaw, Kurzrock, Markee, Novak, Overholser and Nelson, P. E. Smith, Wilson, Zuckermann and others. The vast number of investigations is indicative of the interest which this important problem arouses. The following theories may be mentioned:

- 1) Menstruation is produced by lowering of the estrone level in the blood. This theory is particularly held by Allen, Smith and Engel.

<sup>2</sup>The analyses were carried out by Dr. Stein in the laboratory of Prof. Wertheimer.



- 2) Menstruation is produced by lowering of the progesterone level in the blood.
- 3) Menstruation is initiated by a particular bleeding substance of the anterior pituitary. This theory is, in the main, defended by Hartmann, Firor and Geiling, as well as Wilson and Kurzrock.

I tried, in an experimental way, to study the influence of the gonadotropic factor on the mechanism of the uterine bleeding. The rabbit was chosen as the experimental animal. The sexual cycle in the rabbit runs an absolutely different course from that of the human being; follicular rupture never occurs spontaneously and the cycle runs its course without any bleeding. There is, therefore, no such bleeding mechanism in this animal. I chose the rabbit for this particular reason. I wish to see whether it is possible to produce bleeding from a uterine mucosa which does not bleed physiologically. Should this experiment succeed, it would probably shed a great deal of light on the bleeding mechanism. I want to anticipate the main results of these experiments. By intravenous administration of gonadotropic hormone it was possible to produce extraordinarily large hemorrhages, uprooting the entire mucous membrane, and rupturing into the uterine cavity. Eventually blood was discharged by way of the vagina. The entire process took place in the proliferative mucosa. It was, therefore, a pseudomenstruation. The type of gonadotropic hormone was of no significance. The hemorrhage was produced by prolan from pregnancy urine, as well as by gonadotropic hormone from mare's serum and from the anterior pituitary gland. Bleeding, however, only occurs after intravenous, never after subcutaneous administration. Too small doses only bring about hyperaemia without bleeding. Too large doses of gonadotropic hormone prevent the bleeding, owing to the action of the corpora lutea and progesterone. I have illustrations to show that in the rabbit, which never bleeds spontaneously, an anatomical condition can be produced which resembles—as far as a comparison is permitted—that of menstruation in the woman.

If too large doses of prolan are used the mucous membrane is rapidly transformed into the progestational phase. There is, indeed, marked hyperaemia, but never bleeding. This demonstrates that, in the rabbit, corpus luteum hormone inhibits the bleeding mechanism.

In castrated animals the administration of prolan has no effect on the uterus. This shows that the hemorrhage-producing action of prolan becomes effective by way of the ovary. Which of the two hormones produced in the ovary causes the bleeding? Corpus luteum hormone, as already described above, inhibits the bleeding action. Is it folliculin that brings about the hemorrhage? If varying doses of folliculin are injected intravenously on five successive days into infant rabbits, no bleeding occurs. This might give rise to the assumption that folliculin must be

ruled out as a "bleeding factor", that there must be a third unknown hormone, produced in the ovary, which initiates the bleeding process.

The deductions which I published in the *Journal of Obstetrics and Gynecology of the British Empire* last year are along those lines. Further experiments, however, have demonstrated that estrone, too, is able to induce hemorrhages in the rabbit, if a certain experimental set-up is adhered to. The estrogenic hormone must be injected during the course of twenty-four hours in two portions of 250 international units each. If this is done, after an interval of five days, in the majority of cases, a typical, deeply extending bleeding of the uterine mucosa can be observed.

With regard to folliculin, the experiments show the following facts: A fairly long interval is observed between hormone administration and first hemorrhage. Now the following questions arise as regards this interval:

- 1) Is it the lowering of the estrone level in the blood during this interval that brings about the hemorrhage? Or
- 2) Is the estrogenic hormone transformed into another substance which produces the bleeding? Or
- 3) Does estrogenic hormone or a transformed product of this substance stimulate the action of the bleeding factor in some other gland?

In this connection the pituitary and the adrenals could be considered.

During my stay in this country, I asked Dr. Greep to perform some experiments on hypophysectomized rabbits, on which he will now report.

*Dr. Greep:* Evidence was obtained confirming the observation of Dr. Zondek that uterine hemorrhages simulating true menstruation can be produced in rabbits. The bleeding was observed in infantile rabbits six days after intravenous treatment with estrogen. The possibility of an intermediary action by the pituitary gland was eliminated by the production of hemorrhages in the uteri of hypophysectomized rabbits.

The bleeding was usually confined to the submucosal tissue, though in a few instances blood had escaped into the lumen of the uterus. The bleeding occurs in localized areas which are discernible by macroscopic observation. These areas show necrosis of the uterine epithelium and submucosa.

The opinion was expressed that the bleeding was associated with involution of the uterus after estrogen stimulation and that the postulation of a "third" or hemorrhagenic hormone seems unnecessary at present.

This problem is very important with regard to the menstrual mechanism. In view of these facts, it can be deduced that pseudomenstrual bleeding is produced by a substance which results from the transformation of estrogenic hormone. On the other hand, the menstrual bleeding may be initiated by a product resulting from the transformation of progesterone. In order to throw light upon this question, we injected estrogenic hormone or progesterone into rats, killed the animals after five days, and then prepared a tissue mash which we extracted by means of organic solvents. However, we did not succeed in converting the estrogenic

hormone into a substance able to initiate bleeding. From other animals, however, which had been treated with progesterone, we extracted a substance which actually produced bleeding. However, among ten experiments we succeeded but twice in doing this. There is, therefore, the possibility that progesterone is transformed into another substance which induces bleeding. But these few experiments are by no means sufficient to decide this question.

*Inhibition of menstruation through estrogenic hormone.* Estrogenic hormone, if given in physiological doses, produces proliferation of the uterine mucosa. In castrated women it is able to produce pseudomenstruation. Large doses of estrogenic hormone shift the occurrence of menstruation within the cycle, owing to inhibition of the gonadotropic mechanism of the anterior pituitary. This, in its turn, causes degeneration of the corpus luteum and insufficient or absent progestational transformation of the uterine mucosa. As we were able to demonstrate in 1935, it is possible, in this simple way, to produce artificial amenorrhea, persisting from seven to seventy days. Since it would take too much time to discuss this in detail, I shall restrict myself to reporting one clinical observation:

In the literature it has been pointed out that elimination of the growth hormone of the anterior pituitary has an inhibiting influence on carcinomatous growth. The growth hormone of the anterior pituitary can be eliminated by estrogenic hormone, as has been experimentally demonstrated. Through prolonged administration of estrogenic hormone, I produced dwarfed animals. I attempted to influence the growth of carcinoma in a woman who suffered from numerous metastases of a mammary carcinoma and was in a desperate condition. I gave large doses of estradiolbenzoate. She received 100,000 international units daily for sixty days, a total, therefore, of 6,000,000 international units. The growth of the carcinoma was not influenced in any way whatsoever, and the patient succumbed to the great number of metastases. Before hormone administration menstruation had been normal. Subsequent to the sixty days of treatment she had completely atrophic ovaries. During these sixty days no follicle had ripened, nor had a corpus luteum been formed. The ovaries were those of an old woman. We had, therefore, achieved hormonal sterilization. In the anterior pituitary, an eosinophilic adenoma was found.

There can, therefore, be no doubt that in a normally menstruating woman large doses of estrogenic hormone can inhibit menstruation; this inhibition occurs through the elimination of the gonadotropic hormone, so that neither ripening of the follicles, nor corpus luteum formation takes place.

*Hemorrhages induced by progesterone.* In the preceding paragraphs it has been explained that both estrogenic hormone and progesterone are able to produce hemorrhages in the uterus. Now I shall demonstrate



that even *within* the cycle progesterone is able to induce hemorrhages. Mere chance led me to this observation, when I treated a sterile woman and attempted to achieve better development of the mucous membrane. If ten milligrams of progesterone are injected into a normally menstruating woman on five successive days during the postmenstrual stage, after an interval of sixty hours a bleeding occurs in the intermenstrual stage. This hemorrhage persists for some days. I am inclined to call it intracyclic bleeding. It is interesting that the women, during the period of treatment, feel their breasts become swollen and experience pain in the hypogastric region. All symptoms subside as soon as the bleeding sets in. It is, therefore, possible—and this is most interesting—to achieve bleeding from a proliferative mucosa through progesterone alone. In regard to progesterone, therefore, the mechanism of bleeding does not require the preceding premenstrual development of the mucous membrane.

What happens if progesterone is injected during the intermenstrual phase, at a time when the follicle has already ruptured, a corpus luteum has already developed, and the woman is under the influence of her own progesterone? In this stage progesterone has no effect at all. Menstruation does not occur earlier but appears at the expected time. If, therefore, the organism is already saturated with its own corpus luteum hormone, the hormone which is supplied extraneously can no longer influence the process.

Thus we are able to produce bleeding artificially in the intermenstruum in a normally menstruating woman. During this stage folliculin production is particularly high and the excretion of this substance in the urine, particularly marked. This large proportion of folliculin does not influence the occurrence of the artificially provoked hemorrhage. The intracyclic hemorrhage can, however, be prevented by giving, subsequent to progesterone treatment, on four days in succession, 100,000 international units of estradiolbenzoate. This demonstrates that the mechanism whose action is responsible for the progesterone-hemorrhage is interfered with by estrogenic hormone. The dosage of hormone administered, however, is of paramount importance.

After it had become evident that progesterone was also able to initiate bleeding in the insufficiently developed uterine mucosa, we were greatly interested in studying the effect of progesterone in amenorrhea. The view which has been generally accepted hitherto is the following: in order to initiate bleeding in an amenorrheic woman, first of all the mucous membrane must be developed by means of estrogenic hormone. Only then can progesterone become active. This assumption is not correct. If progesterone *only* is given to an amenorrheic woman, we were able, by the administration of this substance exclusively, to induce bleeding. It is of particular interest that this effect takes place in secondary amenorrhea, but not in primary amenorrhea. This fact permits of the conclu-



sion that a certain amount of folliculin production is nevertheless present in secondary amenorrhea, sufficient, at any rate, to develop the mucous membrane to a certain extent. In primary amenorrhea there is no folliculin production at all.

I should like to quote one more observation belonging to this group of experiments: Last year Inhoffen and Hohlweg succeeded in preparing a substance from testosterone, the ethynyl-testosterone (or pregnen-in-on-ol) which, if given *per os*, exerts the typical corpus luteum effect. I tested this substance in normally menstruating, as well as amenorrheic women. In both we succeeded in producing artificial hemorrhages with five days' treatment with a total of 300 milligrams. If these results find further corroboration, we shall be able to treat certain cases of amenorrhea simply by some pills which the patient would take for five days.

*A theory of menstruation.* I should like to submit to you a theory on the menstrual process but I am fully aware of the fact that it is only a theory, and one which may possibly be erroneous in some respects.

Menstruation is a complex occurrence resulting from the cooperation of the hormones of the anterior pituitary lobe and the ovary. The regulating factor within this cycle is estrin. The estrin level regulates the menstrual cycle as, for example, the mercury level does the thermostat. The high estrin level which exists during the intermenstruum inhibits the activity of Prolan A (follicle ripening hormone). As a consequence of this, Prolan B is brought into action. Now the follicle ruptures and a corpus luteum develops, while at the same time the folliculin level is lowered and, in falling, stimulates again the activity of hormone A. In the corpus luteum, too, estrone (folliculin) is produced at this stage. In this way the very high estrin level which exists a few days before the onset of menstruation blocks the action of the anterior pituitary gland completely, so that the estrin as well as progesterone level are again lowered. After an interval of some days menstruation commences.

In brief:

- 1) Lowering of the estrin level brings the follicle ripening hormone (A) into activity.
- 2) High estrin level inhibits the activity of hormone A.
- 3) Very high estrin level inhibits the activity of both hormones A and B.

What factor actually initiates the onset of the menstrual bleeding has not been explained as yet. There are, however, the following three possibilities:

- 1) The lowering of the hormone level may be the responsible factor;
- 2) During the interval period either estrin or progesterone are transformed into another substance, and this substance may be the initiating factor for bleeding; or
- 3) The lowering of the estrin or progesterone level initiates, in some other gland, the production of the causative factor of bleeding.

It is particularly the hypophysis or the adrenals which must be considered in this connection.

After P. E. Smith, Edgar Allen and Corner had shown that estrin produces uterine bleeding also in monkeys whose hypophysis or adrenals had been previously removed, this theory can no longer be held.

I am not entirely satisfied that the withdrawal of estrin from the blood produces such an active process as menstruation. It is my belief that either from estrin<sup>3</sup> or from progesterone, or from both, a new substance is formed in the body in the interval between its production and its utilization and that this transformed substance causes the bleeding. I am at present working to prove if this view is correct.

In conclusion, I would like to say that I am fully aware of the fact that the clinical and experimental investigations described in this lecture constitute but a small stone in the complicated structure of the problem of the ovarian function and the mechanism of menstruation.

<sup>3</sup> After completing this paper I found in the literature that Smith and Smith had offered a similar theory.

## PRIMARY ANGIO-SARCOMA OF THE SPLEEN

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[From the Medical Service of Dr. B. S. Oppenheimer and the First Surgical Service]

The following case is of interest not only because of the rarity of the pathological character of the lesion, but also because it serves to emphasize the fact that the surgeon is not infrequently confronted with a primary splenic enlargement, the origin of which is obscure and cannot be determined clinically. Under such circumstances splenectomy is indicated.

### CASE REPORT

*History* (Adm. 421662). The patient, a girl of 13 years, was admitted to the Medical Service of The Mount Sinai Hospital on March 21, 1938, with the chief complaint of enlargement of the spleen of one year's duration. Accompanying this enlargement was fairly constant pain in the left upper quadrant and frequent night sweats. There was no jaundice or hematemesis. A careful inquiry into the history of this patient failed to reveal any other abnormal symptoms. The past history was negative.

*Examination.* This was essentially negative except for the finding of an enlarged spleen which filled most of the left upper quadrant and extended downwards as far as the level of the umbilicus. The spleen was firm, somewhat tender, presented rounded edges, and moved with respiration.

*Laboratory Data:* Sedimentation time, 45 minutes. Hemoglobin, 75 per cent; white blood cells, 13,400, (54 per cent segmented polymorphonuclear leucocytes, 1 per cent non-segmented leucocytes, 38 per cent lymphocytes, 5 per cent monocytes, 1 per cent eosinophiles, and 1 per cent basophiles). Mantoux test was positive in 1:1000 dilution. Blood platelets, 300,000; reticulocytes less than 5 per cent. Urine, negative. Wassermann reaction, negative. Urea nitrogen, 13. Blood sugar, 90. Icterus index, 4. An intravenous pyelogram showed displacement of the left ureter by the enlarged spleen. A positive diagnosis could not be made and operation was decided upon because of the persistence of the pain and the progressive enlargement of the spleen.

*Operation* (April 14, 1938). Through a left upper rectus incision with a right angle extension, the peritoneal cavity was opened. The enlarged spleen presented in the wound. It extended downwards to the umbilical line. Its edge was rounded. Its consistency was soft and it was covered with numerous adhesions to the great omentum. The upper pole was densely adherent to the left leaf of the diaphragm. The liver was normal. The vessels in the splenic pedicle were not enlarged and did not contain any thrombi. There was no enlargement of the regional lymph nodes. The exact reason for the splenomegaly could not be determined. At the time of operation it was thought that the enlargement was probably due to intrinsic disease of the spleen, and splenectomy was decided upon. This was done in the usual manner, ligating the pedicle serially with silk, separating the adhesions of the omentum, and also the attachment to the diaphragm. Because of persistent ooze, a piece of

gauze packing was placed against the raw surface in the diaphragmatic region. Convalescence following this procedure was uneventful and the patient was discharged from the hospital twelve days later. The wound had healed by primary union.

*Pathological Examination by Dr. P. Klemperer:* "Specimen consists of a spleen weighing 635 grams and measures 21 x 8 x 4 cm. Scattered over the surface are firm adhesions. The hilar vessels are negative. The capsule is not thickened. The surface of the spleen presents an irregular knobby appearance due to the presence of many small yellowish nodules. The general color is mottled gray, yellow, and pink. Shining through the capsule may be seen many large irregular venous channels which present an angiomatous appearance. The organ cuts with increased resistance. The cut section shows none of the normal appearance of the spleen.



FIG. 1

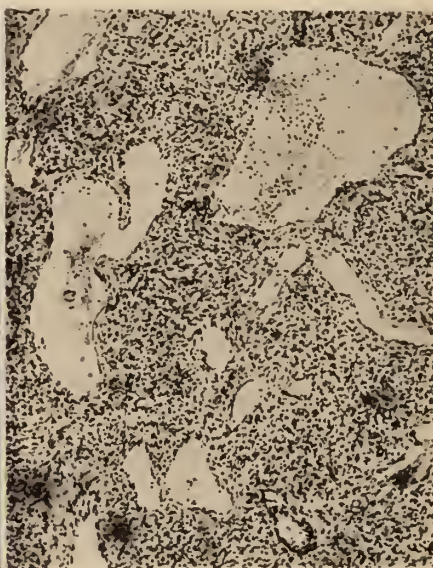


FIG. 2

FIG. 1. Angio-sarcoma of the spleen. Cut section of the gross specimen  
FIG. 2. Photomicrograph showing the histological character of the tumor

Numerous greenish yellow nodules are seen throughout the cut surface. The microscopic picture is that of an angiosarcoma." (Figures 1 and 2)

*Follow-up.* Since discharge from the hospital the patient has done well. She has gained considerable weight and is free of the symptoms which she presented at the time of admission to the hospital. Examination shows a firmly healed abdominal wound. No masses are demonstrable.

#### COMMENT

Although primary sarcoma of the spleen is rare, several varieties of this tumor have been reported. Most of the reported cases fall into the classification of three varieties described by Weichselbaum in 1881.

1. Spindle-cell sarcoma. The structure, in the reported cases, showed



spindle and round cells with trabeculae and solid areas of fibrous tissue. This group includes the angio-sarcomas.

2. The endothelial sarcoma is the most frequent variety. It usually produces multiple nodules in a greatly enlarged organ and metastases are commonly present. The tumor is quite malignant.

3. Primary lympho-sarcoma of the spleen is apparently derived from the lymphoid cells of the pulp or follicles. This tumor produces diffuse enlargement of the organ and the normal structure is largely destroyed by diffuse growth of small or large round cells of the lymphocyte variety. Metastases are common.

The case reported above belongs to the first variety of Weichselbaum's classification. The prognosis for cure seems excellent.

## PSEUDO-POLYCYTHEMIA

FRANK A. BASSEN, M.D., AND HAROLD A. ABEL, M.D.

[From the Medical Services of Dr. George Bachr and Dr. B. S. Oppenheimer]

Polycythemia is generally classified as primary or secondary. In both types there is an absolute increase in the red cell volume. The plasma volume remains remarkably constant. The primary or idiopathic type constitutes a clinical entity, whereas the secondary type is the result of a known cause, usually chronic cardiac disease, or disease of the lungs or pulmonary vessels.

In excessive hyperemesis, or protracted diarrhea, a polycythemic blood picture may ensue. These cases are not truly polycythemic. On the contrary, an actual anemia may exist but the plasma volume is so depleted that a relative increase in the cell volume results. When such a state is present the etiological factor is usually obvious.

In the cases to be presented, the polycythemic blood pictures, and to some extent the clinical findings, suggested the diagnosis of polycythemia vera. However, the blood volume studies revealed the picture of hemoconcentration seen in dehydrated states without the presence of the usual etiological factors.

### CASE REPORTS

*Case 1. History* (Adm. 374714). This patient was an Austrian Jew, 53 years of age, admitted to the service of Dr. B. S. Oppenheimer on December 18, 1934. For a year prior to admission, increasing drowsiness and difficulty in concentration were noted. In the same period a chronic cough, thought to be due to excessive smoking, had increased in intensity. There were also infrequent attacks of nocturnal dyspnea. For about six months the patient was aware of bluish discoloration of the face, hands, and feet, and suffusion of the conjunctivae.

*Examination.* The patient was a short, extremely plethoric, cyanotic man with a short neck and a very obese abdomen. The eye grounds showed greatly engorged tortuous veins. The lips, gums, palate, and mucous membranes of the mouth were intensely cyanotic with a deep reddish hue. The lungs revealed unimpaired resonance and distant breath sounds. There were coarse râles at the bases which were rather high because of the extreme obesity of the abdomen and moved only slightly on respiration. The size of the heart could not be determined but there seemed to be some enlargement to the left. The rhythm was regular, the sounds of fair quality, and there was a soft, systolic murmur at the base. The blood pressure was 120 systolic and 80 diastolic. The abdomen was greatly enlarged, and therefore palpation was difficult. No masses or viscera were felt. The extremities showed no clubbing or edema and the peripheral pulses were all patent. The patient was definitely overweight for his height, being barely five feet tall and weighing 195 pounds.

During the examination, the patient fell asleep several times.

*Laboratory Data:* The original blood examination was as follows: hemoglobin, 141 per cent; red cells, 7,100,000; white cells, 7,200; platelets, 280,000; polymorphonuclear neutrophils: non-segmented 2 per cent, segmented 71 per cent; eosinophils, 1 per cent; lymphocytes, 15 per cent; monocytes, 9 per cent; myelocytes, 2 per cent; normoblasts, 2 per 100 white cells. The blood volume<sup>1</sup> at that time showed total blood volume, 8,000 cc.; cell volume (60%), 4,800 cc.; plasma volume (40%), 3,200 cc.; volume per kilogram, 90 cc.

The urine, blood chemistry, and serology were negative. The basal metabolic rate was minus 7. An electrocardiogram revealed no marked deviation from normal. The chest X-ray examination showed enlargement of the heart, particularly to the right, engorged pulmonary vessels, widening of the superior mediastinum and displacement upward of mediastinal structures from pressure of an enlarged abdomen.

*Course.* The house physician's diagnosis was polycythemia vera; obesity; and chronic bronchitis and emphysema. The patient was phlebotomized four times with withdrawal of 350 to 450 cc. on each occasion. After this, the cell volume remained 60 per cent of the total but the unit volume had dropped to 70 cc. per kilogram. Despite thyroid therapy, he failed to lose weight and remained lethargic. He was discharged January 6, 1935 with a final diagnosis of chronic bronchitis and emphysema, obesity and polycythemia; no decision whether the polycythemia was primary or secondary in type.

Since his discharge he has been followed in the hematological clinic and has been admitted to the hospital on two occasions for more thorough follow-up. He continued to exhibit lethargy and polycythemia—manifesting only mild improvement from occasional phlebotomies. A blood volume taken in August 1935 showed 84 cc. per kilogram with the hemoglobin 115 per cent at that time. The relative cell volume was 55 per cent. Definite improvement was noted after a weight reduction of some 30 pounds in the latter part of 1936. His general appearance was improved, he became less somnolent and felt better. The blood picture remained unchanged, however. For about a year and a half he failed to report to the clinic but reappeared in December 1938. During the interval, he had felt rather well, was less lethargic, and maintained his weight loss. A blood examination on February 25, 1939 showed hemoglobin, 110 per cent; red cells, 5,500,000. Blood volume studies showed the relative cell volume to be 52.5 per cent and the unit volume 71 cc. per kilogram. A re-examination of the chest showed the lung fields to be clear; the heart shadow was not increased, though there was a straight left border.

*Case 2. History* (Adm. 431565). This patient was a 43-year old American-born man, admitted to the service of Dr. George Baehr in November 1938. He had always been an excessive smoker. For ten years he suffered from severe, right, hemicranial, throbbing headaches, sudden in origin. They were often accompanied by blurring of vision and occasionally by vomiting. Twenty-seven years before admission he suffered a mild frost-bite of the right foot involving chiefly the first and second toes. This condition cleared up promptly.

About seven months before admission, he began to notice episodes of marked pain and a burning sensation in the toes of the right foot and calf and, to a much lesser degree, in the left foot. This pain increased when the foot was in a dependent position and could be relieved by elevation and massage of the part. There was apparently no relation of these attacks to temperature changes. During these episodes

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<sup>1</sup> The blood volume determinations were made according to the method of Keith, Rowntree and Geraghty (1).

definite cyanosis of the foot was noticeable. The last episode began seven weeks before admission and continued without interruption. The big toe of the right foot remained cyanotic and began to ulcerate. During this seven month period paresthesia and cyanosis of the fingers was noted, in association with the foot symptoms. The patient also noted a gain in weight. He had also experienced rather frequent attacks of vertigo and dyspnea.

*Examination.* The patient was a well-developed, slightly obese, florid-appearing male. He was 66 inches in height and weighed 185 pounds. The fundi showed early arteriosclerotic changes. There was slight enlargement of the heart and a blood pressure of 176 systolic and 104 diastolic. The lungs were clear and the abdomen entirely negative. The peripheral pulses were all patent. The right foot and toes were warm to the touch except for the large toe which was cyanotic, cold and tender. On the mesial aspect there was one area which showed a small ulceration.

The blood count on admission was as follows: hemoglobin, 116 per cent; red cells, 5,926,000; white cells, 7,500; platelets, 280,000; polymorphonuclear neutrophils: non-segmented 2 per cent, segmented 65 per cent; eosinophiles, 2 per cent; basophiles, 1 per cent; lymphocytes, 28 per cent; monocytes, 2 per cent. The blood volume results were total blood volume, 6,380 cc., relative cell volume, 54.5 per cent; 76 cc. per kilogram.

Venous pressure, circulation time, blood chemistry, and basal metabolic rate were all normal. The skin temperature of the right toe was somewhat higher. The electrocardiogram showed a left ventricular preponderance. A study of the end capillaries of the nail beds showed them to be abnormal. There was an increase in the size and number of capillaries. The tips were bulbous and filled with semistatic blood corpuscles. Oscillometer readings were repeatedly normal.

*Course.* The house physician's diagnosis was (1) polycythemia vera ((a) erythromelalgia with acrocyanosis, (b) thrombosis of digital artery of the hallux of the right foot with local gangrene, (c) hypertension, (d) migraine) and (2) hypertensive cardiovascular disease. Treatment was directed to local antisepsis, postural exercises and bed rest. Under this regime, the big toe improved progressively and finally healed completely. He was discharged after a month's confinement. The discharge diagnoses were (1) hypertension, essential and (2) angioneurosis. For a period of two months he was asymptomatic and was able to attend his duties. In March 1939 he again developed burning pain in the feet and toes, especially in the right big toe. This again became cyanotic and finally developed a paronychia infection. Because of this he was re-admitted to the wards on April 17, 1939. All findings were similar to those of the previous admission. At this time his hemoglobin was 115 per cent and red cell count, 5,900,000. The unit blood volume was 64 cc. per kilogram with an hematocrit of 50.5 per cent.

#### DISCUSSION

These cases must first be considered in the light of our present understanding and classification of polycythemia. *Case 1* was thought to be of the primary idiopathic type until volume studies were made. Since blood volume determinations are calculated on body weight, it may be suggested that if calculated on normal weight figures, the results would be higher and possibly conform with what would be expected for polycythemia vera. Such a contention would have some foundation. Rowntree, Brown and Roth (2), in their blood volume studies, found that in obesity there was an increase in the mean total blood volume as compared



to the mean normal figures but it was not proportionate to the gain in weight. Thus a 60 per cent weight increase may show only a 20 per cent volume increase. However, the cell plasma volume ratio in these cases was normal. In no case was there an increase in the hematocrit readings. In *Case 1* several determinations were made. In all, the volume per kilogram was normal or subnormal. In the last study, made after a weight loss of 30 pounds, the volume per kilogram showed no increase and was, in fact, found to be lower than on the previous determinations. It would appear, therefore, that obesity played no rôle in falsifying the figures in this case, and certainly if the polycythemia was of the primary type the last determination should have yielded higher results. In an attempt to determine the rôle of obesity in true polycythemia, one of our cases with this disease was selected for study. Her height was 62 inches and her weight 175 pounds. She had received X-ray therapy and at the time these studies were made her polycythemia was only moderate. The hemoglobin was 107 per cent and the red cell count 5,440,000. The hematocrit reading was 48.5 per cent. These figures are not truly polycythemic but may be compared to those of *Case 2*. The studies in this case revealed a blood volume of 103 cc. per kilogram of body weight with a plasma volume of 56 cc. per kilogram of body weight. These findings seem perfectly compatible with the hematological picture, and are apparently not modified to any great extent by the patient's weight. The plasma volume may be considered to be within normal limits in contrast to the marked depletion in the cases reported. It may be stated here that obesity is unusual in polycythemia vera. Patients with this disease are more commonly of the spare type. They are often well developed and well nourished but are rarely obese. In the last analysis, however, we must rely on our blood volume findings to differentiate these cases from polycythemia vera for unless the total red cell mass is absolutely increased this diagnosis cannot justifiably be made.

The possibility of the polycythemia being secondary was considered seriously in *Case 1*. He had evidence of chest pathology and on his first admission chest X-ray studies were reported as showing pulmonary emphysema and cardiac enlargement. However, later plates, after weight loss, showed clear pulmonary fields and a heart not unusual except for a straight left border. Since his first admission, in 1934, nothing has developed to substantiate the assumption that there was pulmonary or cardiac pathology of a degree sufficient to produce the polycythemia.

Hemoconcentration has been noted by Silbert, Kornzweig, and Friedlander (3) to be present in a certain percentage of their cases of thromboangiitis obliterans, and they consider it to bear a definite relationship to the underlying disease. Roth, Maclay, and Allen (4) have found it in a few cases of this disease but think it too inconstant a finding to be of importance.

In their studies on blood volume determinations, Rowntree, Brown and Roth describe briefly a case remarkably similar to *Case 2*. A blood volume determination was made to establish the diagnosis of polycythemia vera. The cell volume was high (54%) but the volume per kilogram was low (74 cc.). They defined this blood volume finding as hypovolemic polycythemia.

The cases presented emphasize the importance of complete volume studies where the diagnosis is doubtful. Certainly, in these patients with their florid complexions and the high red cell, high hemoglobin, and high relative cell volume figures, polycythemia vera seemed a very likely diagnosis. However, by virtue of the definition of this disease, such a diagnosis becomes untenable where the red cell mass is shown not to be increased.

It is interesting to note that aside from the blood volume similarity these cases presented other common findings, probably not sharply defined, but nevertheless present. Both noted a tendency to gain weight and complained of dyspnea which seemed out of proportion to the degree of obesity. Evidence of peripheral vascular disease was manifested in *Case 2* in the vessels of the extremities and in *Case 1* it seems not improbable that the somnolence was due to involvement of the cerebral vessels. What the relationship of these findings are to one another, if they are related, cannot at this time be stated.

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## A CASE OF HYPO-PARATHYROIDISM TREATED WITH DIHYDROTACHYSTEROL<sup>1</sup>

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*[From the Medical Service of Dr. George Baehr, the Surgical Service of Dr. John H. Garlock, and the Endocrine Clinic]*

The case here presented is one of long-standing parathyro-privic disease which followed subtotal thyroidectomy for hyperthyroidism. Huge doses of calcium salts and parathormone, as well as five parathyroid transplants, failed to afford the patient relief. She presented active signs and symptoms of tetany at a serum calcium level of ten. Satisfactory clinical results in this instance were obtained only when dihydrotachysterol was used as a therapeutic agent.

Dihydrotachysterol was introduced by Holtz (6) in 1933 for the treatment of chronic diseases associated with low serum calcium. Mild cases of hypo-parathyroidism respond to a diet low in phosphorus and high in calcium, supplemented by calcium salts, such as the lactate (1). In the more severe forms, this has been insufficient to elevate the blood calcium to a symptom-free level. Parathyroid extract has been shown to have the following disadvantages:

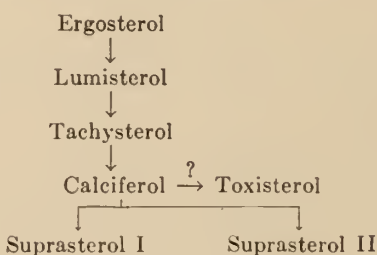
- 1) the necessity of parenteral administration;
- 2) the expense;
- 3) the transiency of action, producing its maximum effect in six hours, becoming ineffectual after twelve to twenty hours;
- 4) the liberation of calcium from the bones produces extensive demineralization;
- 5) the development of tolerance to the drug so that the dose must be continuously increased (in some cases complete refractoriness may ensue (2));
- 6) the theoretical possibility that continuous administration of the hormone might inhibit any action or regeneration of any remaining parathyroid tissue.

The combined use of vitamin D and calcium by mouth to promote the absorption and retention of the calcium is of definite value. Recent investigations indicate that the vitamin can exert its specific action without the intermediate action of the parathyroid glands and toxic symptoms of

<sup>1</sup> We wish to acknowledge the cooperation of Dr. Sobotka in the laboratory determinations and of the Winthrop Chemical Company in furnishing us with A. T. 10 and crystalline vitamin D.

hypervitaminosis may be induced in parathyro-privic animals. Boothby and Davis (3) have claimed good results in most cases in which cod-liver oil and calcium were employed. According to Klatskin (4), contradictory findings by other investigators can be attributed to either inadequate dosage of the vitamin or the use of an impure product. In three cases of hypo-parathyroidism carefully studied by him, crystalline vitamin D in daily doses of 300,000 units rendered the patients symptom-free and restored the blood calcium to normal, after an ineffectual control period during which commercial viosterol was given.

In 1927 there were prepared for the first time highly active agents affecting calcium and phosphorus metabolism through the action of ultra-violet rays on ergosterol. Six isomers were isolated:



Of these, calciferol, lumisterol and the two suprasterols have been crystallized (7). These sterols differ from each other in their effects, only tachysterol, calciferol and toxisterol being pharmacologically active. Calciferol (vitamin D<sub>2</sub>) is the most potent antirachitic agent; the other two have little antirachitic virtue but exert powerful effects on calcium metabolism. Holtz in 1927 (8) attributed the toxic symptoms of hypercalcemia, obtained through the administration of large doses of irradiated ergosterol, to these other non-antirachitic sterols—the so-called “calcinose” factor—because through hydration or heating of the irradiated ergosterol, the antirachitic factor was destroyed, whereas the toxic or serum calcium elevating factor remained.

Dihydrotachysterol was obtained from unstable tachysterol by treatment with nascent hydrogen and, dissolved in oil, was marketed as A. T. 10 (anti-tetany factor 10). By 1938 several hundred cases of low calcium disease had been treated with uniformly good results. The metabolic actions of dihydrotachysterol were studied by Albright and his co-workers (9) in 1938. They found that its primary effect was to increase the urinary phosphorus and decrease fecal calcium. This leads secondarily to a rise in serum calcium and fall in blood phosphorus. A tertiary effect which may occur, concomitant to the rise in serum calcium, is an increased output of urinary calcium. Calcium absorption from the bowel is also increased. Crystalline vitamin D (vitamin D<sub>2</sub>, calciferol) has qualitatively the same effect but is slower in action. The poor antirachitic



effect of dihydrotachysterol is attributable to its great effect on urinary phosphorus excretion. In its action, it resembles parathormone with the added virtue of promoting calcium absorption and retention. Albright et al. (10) have diagrammatically compared the three substances:

	Calcium Absorption	Phosphorus Excretion in Urine
Vitamin D.....	xxx	x
Dihydrotachysterol.....	x	xxx
Parathyroid extract.....	0	xxxx

As marketed under the trade name of A. T. 10, one cubic centimeter of the oily solution represents in effect about 40 units of parathormone and 200 "toxic border units" of Holtz. (A toxic border dose is the smallest amount which, on daily administration to mice, would cause a loss of weight of about 12 per cent or more within twelve days. A Collip unit of parathyroid extract equals one one-hundredth of the amount necessary to raise the blood calcium 5 mg. per cent, fifteen hours after injection into a dog weighing 20 kg. (11).) When taken by mouth, the action of A. T. 10 begins usually after two days, with maximum effect in four to seven days, while the end effect is reached in one to three weeks.

It is advisable to administer the drug perorally along with calcium salts by mouth. The dosage, contraindications, and signs of toxicity due to overdosage have been outlined by Holtz in his numerous publications. The action of the drug is antagonized by follicular hormone; consequently in pregnancy the dosage must be tremendously increased. A small group of patients are hyposensitive to its action, which reaction Holtz (12) attributed to deficient absorption, due to poor pancreatic function. For these patients he recommends pancreas preparations by mouth.

#### CASE REPORT

*History* (Adm. 407907). The patient was a twenty-eight year old, white American girl. She was born in Ohio, lived from the age of six months to eleven years in Michigan, and then returned to Ohio. Her delivery was described as spontaneous, full term, and normal. She had measles at the age of four, and chickenpox and pertussis at five.

At the age of eighteen she manifested symptoms of acute thyrotoxicosis with cardiac palpitation, nervousness, dyspnea and vertigo on exertion, fatigability and weight loss. Her basal metabolism at that time was plus fifty-four and in March, 1931, after preliminary lugolization, a subtotal thyroidectomy was performed in an Illinois hospital. Her postoperative course was exceedingly stormy. The complications resultant from the operation included postoperative exophthalmos associated with myxedema, injury to the right recurrent laryngeal nerve, and severe hypoparathyroidism. Her voice returned in a modified form only six months after the operation. Her myxedema has required continuous thyroid therapy until the present writing. Her basal metabolism six months after the operation was minus thirty-one, and her daily ration of thyroid was approximately six to eight grains. Within a short time after the operation she developed severe exophthalmos which has

receded to some extent in the past few years. In November, 1932, a paratracheal adenoma was removed, and in February, 1934, six small, bluish cervical cysts were removed in an Illinois hospital (no pathologic report was available).

The major symptoms which have incapacitated the patient since the operation have been attributable to a diminution in parathyroid function. Twelve hours after the operation the patient had her first severe attack of tetany. She was placed on a regime of calcium lactate by mouth and parenteral parathyroid extract, but for ten months she was confined to bed with severe tetanic spasms, constant paresthesias, irregular minor muscular contractions, diplopia and progressive edema of the body. In January, 1932, ten months after the operation, her blood calcium was 4.3 mg. per cent, and she was given 60 grams of powdered calcium lactate by mouth and small doses of calcium gluconate intravenously each day. For the succeeding three and one-half years the patient spent most of her time in bed, for the slightest exertion precipitated violent tetanic attacks. She had paresthesias almost continuously, frequent choking and vomiting spells, difficulty in breathing and a sensation of compression over the precordium. In July, 1935, her serum calcium was 6.1 and she manifested slight improvement upon the addition of parathyroid extract (approximately one hundred to three hundred Collip units daily), ammonium chloride in six gram doses and approximately five grams of calcium gluconate intramuscularly, to the huge doses of calcium by mouth.

In October, 1936, she was observed at the Presbyterian Hospital, New York City. She was maintained on a high calcium diet, with parathormone. Her serum contained:

<i>Date</i>	<i>Calcium mg. %</i>	<i>Phosphorus mg. %</i>
10/31/36	12.6	3.2
11/ 3/36	8.9	2.9
11/ 5/36	8.9	4.0
11/ 9/36	9.5	3.9
11/12/36	8.0	3.0

She was considered a case of postoperative tetany, with comparatively high serum calcium and glandular transplant therapy was recommended.

In December, 1936, she entered this hospital, and was observed on the service of Dr. George Baehr. Here a moderate exophthalmos, a small nodule, one centimeter in diameter, to the left of the trachea, and a persistent Chvostek were noted. She also exhibited numerous attacks of tetany on the ward. Her basal metabolism shortly after admission to the hospital was plus seven (patient was taking three grains of thyroid daily). Blood calcium estimations were done routinely:

<i>Date</i>	<i>Calcium mg. %</i>	<i>Phosphorus mg. %</i>
12/17/36	9.7	
12/19/36	8.5	3.9
	8.4	7.7 (during attack of tetany)
12/28/36	10.5	
1 /20/37	11.3	3.8
2 /2 /37	10.3	

Other chemical findings at this time included blood urea nitrogen, 10.0 mg. per cent; cholesterol, 210 mg. per cent; sugar, 75 mg. per cent; CO<sub>2</sub> combining power, 57.5 vol. per cent; chlorides, 565 mg. per cent; total proteins, 6.9 per cent; albumin, 4.9 per cent; and globulin, 2.0 per cent. The Wassermann test was negative. A tourniquet test was negative.

In February, 1937, she received two parathyroid grafts, and a third in May, 1937. The transplantations were performed on the service of Dr. John Garlock.

There was no improvement and she was observed at Presbyterian Hospital in

December, 1937. Without any medication, her serum calcium fell to 6.0. She was given 400 units of parathyroid extract and 10 cc. of calcium gluconate parenterally, with large doses of calcium by mouth, and her serum calcium rose to 8.5 within twenty-four hours. In May, 1938, two more parathyroid transplantations (according to the method of Stone) were performed at Presbyterian Hospital.

Between May and September, 1938, the patient treated herself, taking daily 5 grains of thyroid, 60 grams of calcium lactate, 2 grams of ammonium chloride, 12 grains of suprarenal concentrate (Armour's), and 10 to 20 cc. of calcium gluconate by hypodermic injections, along with 100 to 400 units of parathyroid extract (Lilly). In September she was first observed in the Endocrine Clinic of the Out-patient Department of The Mount Sinai Hospital.

Her general physical condition was good. There was moderate exophthalmos. The Eye Department found the exophthalmometric readings at 93 mm. to be  $23\frac{1}{2}$  on the right and  $20\frac{1}{2}$  on the left. There were anterior and posterior cortical spoke-like cataracts. The fundi were normal. Heart and lungs were normal, and examination of the abdomen revealed no abnormality. The small paratracheal nodule described two years before was still palpable. X-ray examination of the long bones showed no osteoporosis, and that of the sella turcica showed no abnormalities. There was some thickening of the inner table of the skull, particularly in the frontal and occipito-parietal regions. The patient had complained of frequent ecchymoses following slight trauma. The tourniquet test was positive; the hemoglobin was 86 per cent, and the white count, the differential, and the platelet count were normal.

There was a positive Chvostek. A Trousseau sign could be readily elicited, and on one occasion in the Clinic the patient suffered a severe attack of tetany with carpopedal spasm and opisthotonos.

The patient was observed for two weeks, during which time her blood calcium was reported as 8.5, with a total protein of 7.0. On September 14 she began to take 1 cc. of A. T. 10 (0.5 mg. per cent dihydrotachysterol per cc. of oil), along with a daily ration of 30 grams of calcium lactate by mouth, 1 grain of thyroid, 20 cc. of calcium gluconate by hypodermic injection. No real improvement was observed until October 4. She received 66 cc. of A. T. 10 over a test period of forty-eight days. Blood chemistry findings throughout this period were:

Date	Calcium mg. %	Phosphorus mg. %	Total Protein %
9/14/38	11.2		6.1
9/20/38	8.4		6.1
9/28/38	9.3	2.5	6.1
10/12/38	10.0	3.0	
10/19/38	12.4	2.3	

She then received no A. T. 10 for seven days, and her serum calcium on October 2 fell to 10.9 mg. per cent, with a total protein of 6.9 per cent. For the next four weeks she received a daily dose of 1 cc. of A. T. 10, with the following results:

Date	Calcium mg. %	Phosphorus mg. %
11/ 9/38	9.9	3.1
11/15/38	11.9	2.8
11/25/38	11.5	3.0

She then received no A. T. 10 for forty-six days. Through this period she received 2400 units of parathyroid extract.

Date	Calcium mg. %	Phosphorus mg. %	Total Protein %
12/ 7/38	10.0	2.4	
12/21/38	9.2	2.1	6.4
12/30/38	9.4		6.5

For the following eleven days, instead of A. T. 10 she received 4,500,000 units of crystalline vitamin D. During this period the patient felt extremely ill, with frequent muscular spasms and general depression. Despite this medication her calcium rose only to 10.2 mg. per cent.

On January 11, 1939 the patient began to take approximately three-quarters of a cubic centimeter of A. T. 10 daily, along with her regular doses of calcium by mouth and 10 to 20 cc. of calcium gluconate parenterally.

<i>Date</i>	<i>Calcium mg. %</i>	<i>Phosphorus mg. %</i>	<i>Total Protein %</i>
1/25/39	12.0	3.2	
2/ 1/39		2.2	
2/ 8/39	10.7	3.2	6.7
3/ 1/39	10.9	2.5	
3/15/39	10.9	2.8	

On March 29 the serum calcium rose to 14.4 mg. per cent.

The patient was last seen on April 2, 1939. At that time she claimed that she felt better than she ever had in the past eight years. Her facial edema had almost disappeared. There was no diplopia, nausea, or severe attacks of tetany. The paresthesias had almost completely disappeared and her muscular control had markedly improved. Her major complaint, that of difficulty in breathing, had been completely relieved. At the time when her blood calcium was 14.4 mg. per cent the patient had no symptoms or signs of toxicity but a Chvostek could be elicited even at this high serum calcium level. She has found it impossible to diminish her daily ration of about 35 grams of calcium salts.

#### COMMENT

The case is unusual because of the relatively high serum calcium levels at which symptoms persist and the exceedingly large doses of calcium along with dihydrotachysterol necessary to maintain this patient at a symptom-free level.

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## IMPROVEMENT IN TWO CASES OF DIFFUSE SCLERODERMA BY THE USE OF DIHYDROTACHYSTEROL (A. T. 10)

### PRELIMINARY REPORT

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The treatment of diffuse scleroderma has been generally recognized to be a difficult and discouraging problem. In spite of various therapeutic measures, most cases have slowly progressed until the unfortunate victims have become completely crippled and helpless. In recent years the chief methods employed have been sympathectomy (1), parathyroidectomy (2 and 3) and iontophoresis (4) with mecholyl. While some improvement has been reported in patients treated by all of these procedures, none of them has resulted in complete cure, and numerous failures have occurred.

The typical case of diffuse scleroderma presents such characteristic features that its recognition is simple. Beginning usually as a hard non-pitting edema of the skin of the hands, it progressively involves the face, neck, chest, and extremities. The expression of the face changes, the features become less mobile, and gradually a fixed, mask-like facies develops. The mouth is drawn, the ability to open it is restricted, and the lips are thinned. The immovability of the eyelids contributes to the loss of expression. The hands become progressively crippled by contractures of the fingers and ulcerations of the tips. In general, the skin over the affected parts takes on a leathery, or board-like, quality. Later it becomes atrophic and fixed to the underlying subcutaneous tissues. Occasionally there is difficulty in swallowing. Raynaud's phenomena are frequently found to be associated.

The etiology of scleroderma is uncertain. Burch (5) has published a fairly good review showing the extent of our present knowledge. Recent investigators have focussed their attention on calcium metabolism, and studies have shown that the calcium content of the skin is increased in some cases by 20 to 30 per cent (6, 7).

Dihydrotachysterol has been used by Holtz (8) in the treatment of tetany, and by Schmidt-La Baume (9) in cases of impetigo herpetiformis with hypocalcemia. Hummel (10) treated two cases of questionable scleroderma with marked improvement. The one adult patient was a mild case which lacked most of the typical features of the disease. The other patient was an infant, and this case was more likely an instance of sclerema neonatorum rather than scleroderma.

In this report we are presenting the results obtained in two patients with typical scleroderma who were treated with dihydrotachysterol.

#### CASE REPORTS

*Case 1. History* (Adm. 449632). E. S., female, whose present age is 44, was first seen in December 1935, with complaints of blue and infected fingers. She presented the typical picture of scleroderma. A parathyroidectomy was done in this hospital in January 1936, and no improvement was noted during the next twelve months. In January 1937, a right cervico-thoracic ganglionectomy was performed, but this procedure also failed to improve the condition. In January 1938 she began treatment under the supervision of the Peripheral Vascular Clinic in the Out-Patient Department of the Hospital. She received intensive iontophoresis, with mecholyl for three months, then with histamine for several months, and a second course of mecholyl therapy in August 1938. During this period of treatment some improvement in the skin condition was noted. She was then given a series of injections of pancreatic



FIG. 1



FIG. 2

tissue extract for six months, but no effect was produced. She was readmitted to the Medical Service of Dr. George Baehr on December 7, 1939.

*Examination.* At this time she presented the typical appearance of advanced scleroderma. The face was almost expressionless, the skin was tight, hard, pigmented, and atrophic; the eyelids were thickened, the mouth drawn and wrinkled, the lips thin. (Figs. 1 and 2). The skin of the neck and chest was involved. The hands were badly crippled. There were contractures of several fingers of both hands, impaired ability to completely flex or extend the fingers, ulcerations on the tips of several fingers, marked thickening, atrophy, and tightness of the skin. The lower extremities were similarly involved, but to a lesser extent.

*Laboratory Data.* These are presented in Table 1.

Treatment was begun with 1 c.e. of dihydrotachysterol daily. After one week of treatment slight improvement was noted, and as the treatment was continued, the improvement became more and more pronounced. After four weeks of therapy the dosage was reduced to  $\frac{1}{2}$  c.e. daily. At the end of six weeks the patient's facial mobility was greatly improved; the mouth could be opened more widely, and changes in expression were striking. (Figs. 3 and 4). The skin was softer and the atrophy

was much reduced. The mobility of the fingers was increased, the ulcerations were all healed, and the sensitiveness of the tips of the fingers was lessened. The whiteness of the distal portions of the fingers was replaced by a more natural color. The patient also felt that her condition had been greatly improved.

*Case 2. History* (Adm. 449837). J. A., male, age 55, a pharmacist, was first seen in the Peripheral Vascular Clinic of this hospital in October 1939, with a typical advanced scleroderma of thirteen years' duration. He had a very painful, extensive ulcer on the left index finger, with exposure of the underlying bone. He was ad-

TABLE 1  
*Calcium balance studies (3 day period)*  
Calcium intake daily: 100 mg.

DATE	BLOOD CALCIUM	BLOOD PHOS- PHORUS	TOTAL CALCIUM INTAKE (3 DAY PERIOD)	TOTAL URINARY CALCIUM OUTPUT	CALCIUM BALANCE	COMMENTS
Case 1						
	mg. %	mg. %	mg.			
12/10/39	10.3	4.6	300	252	+48	Control period.
12/29/39	10.2	4.1				After 10 days of treatment with 1 c.c. of A.T. 10 daily.
1/19/40	10.3	3.8				After 1 month of treatment with 1 c.c. of A.T. 10 daily.
Case 2						
12/13/39	10.1	3.5	300	241.5	+55	Control period.
12/29/39	9.0	4.2				After 10 days of treatment with 1 c.c. of A.T. 10 daily.
1/ 9/40	10.6	4.1				After 3 weeks of treatment with 1 c.c. of A.T. 10 daily.
1/31/40	10.3	3.2				After 6 weeks of treatment with A.T. 10, 1 c.c. daily for 3 weeks, then $\frac{1}{2}$ c.c. daily.

mitted to the hospital for amputation of this finger. The wound healed slowly. He returned to the hospital in November 1939 and a parathyroidectomy was done by Dr. Garlock. He was then observed in the Peripheral Vascular Clinic for about 4 weeks and no improvement was noted. He was readmitted to the Medical Service of Dr. George Baehr on December 12, 1939.

At this time he showed the typical appearance of an advanced scleroderma of the face, neck, chest, hands, and feet. The stump of the left index finger still showed a small granulating wound. There was a small ulcer on the right heel. He had marked thickness and inflexibility of the skin over the fingers of both hands. The laboratory findings are noted in Table 1.

Treatment with dihydrotachysterol was begun with 1 c.e. daily. As in the previous case, improvement began to be noted in about a week, and became steadily more marked as the treatment was continued. The ulcerations healed in two weeks, the mobility of the fingers was greatly increased, and the subjective sensation in the skin of the face became more natural. After six weeks of treatment this patient also felt that his condition had been greatly improved.

#### DISCUSSION

It was fortunate that these two patients were in the wards of the hospital where their progress could be watched by many critical observers. It was the unanimous opinion that striking improvement had taken place in both cases. No conclusion as to the value of this form of treatment can be ventured with so limited an experience. Many other patients, and particularly such who have had no operations for scleroderma, must be



FIG. 3



FIG. 4

treated and followed for longer periods to establish the value of this drug. A preliminary report of these two cases is presented because the results obtained in this brief time are so promising.

Dihydrotachysterol (A.T. 10) is a powerful drug, of unknown potentialities. Overdosage may cause toxic effects and may be extremely dangerous. For this reason it would be wiser, for the present, to limit treatment to patients who are under hospital observation, where adequate laboratory controls are available.

#### CONCLUSION

The administration of dihydrotachysterol in two advanced cases of scleroderma resulted in striking clinical improvement.

We wish to thank Dr. George Bachr for his kindness and help in the study of these patients.



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# FULMINATING STAPHYLOCOCCUS AUREUS SEPSIS TREATED WITH STAPHYLOCOCCUS ANTITOXIN AND SULFAPYRIDINE

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The following is a relatively rare instance of recovery from a fulminating *Staphylococcus aureus* septicemia with metastases to bones, joints, lungs and skin. In the treatment of the case, surgery, repeated blood transfusions, staphylococcus antitoxin and sulfapyridine were employed. A review of the clinical course seems to indicate that the administration of staphylococcus antitoxin in combination with sulfapyridine evoked a highly beneficial response.

## CASE REPORT

*History* (Adm. 433607). A boy, 12 years old, was admitted to the hospital on December 16, 1938. Six weeks previously, he had sustained a laceration over the left elbow. This had drained persistently and showed but little tendency to heal. However, no medical treatment had been sought. Three days before admission, the patient had a severe chill and his temperature went up to 104°F. Despite aspirin, the patient's temperature rose another degree and he became delirious. Hospitalization was then recommended.

*Examination.* The patient was extremely toxic. He responded poorly to questions and, at times, was delirious. Temperature was 106°F.; pulse rate, 150 a minute; respirations, 24 a minute. On his left elbow there was a small crusted erosion of the skin. At the middle third of the left clavicle there was an area of swelling which was exquisitely tender to touch. There were no other abnormal physical findings.

*Laboratory Data.* White cell count, 7,800 per cu.mm.; differential, 84 per cent polymorphonuclear neutrophils with a marked shift to the left; hemoglobin, 83 per cent. Blood culture (reported three days after admission): 70 colonies per cubic centimeter of *Staphylococcus aureus* A. Urine: albumen, one plus; microscopic, one white blood cell and one red blood cell per high power field. X-ray examination of the chest and both clavicles was negative.

*Course.* A diagnosis of acute osteomyelitis of the left clavicle was made. Though it was realized that the clavicle was probably only one metastatic focus of a generalized septicemia, exploration was felt to be indicated and was immediately performed. A subperiosteal abscess at the middle third of the left clavicle was found. A small amount of pus was evacuated, and the marrow cavity opened and drained. On the day after the operation, the elevation in temperature persisted and toxicity and hallucinations became more severe. A macular skin eruption developed chiefly on the extensor surfaces of both legs with a few lesions on the trunk, arms and scalp. A culture made from the pus obtained at operation was reported as showing *Staphylococcus aureus* A. The following therapy was then instituted: 1) daily small blood transfusions; 2) staphylococcus antitoxin intravenously, 20,000 units daily; 3) sulfapyridine with an initial dose of three grams and continuing with one gram every

four hours. During the next four days, the temperature continued at the same level (105°F.) with occasional drops to 103°F.; the delirium persisted. Pustules developed at the site of the macular skin lesions, culture of which also yielded *Staphylococcus aureus*. The patient became increasingly dyspneic with respirations occurring at the rate of 60 a minute. Oxygen was given via a nasal catheter. An X-ray examination of the chest, taken at the bedside on the fourth day in the hospital, was reported as suggesting the presence of infiltrations in the right lower lobe. Three days later following the intravenous administration of 10,000 units of staphylococcus antitoxin, the patient developed a severe chill which lasted for more than thirty minutes. His temperature rose to 108°F. Four hours later, it had dropped to 98°F. and thereafter did not rise above 103°F. By this date, in all, five transfusions, 80,000 units of staphylococcus antitoxin and 20 grams of sulfapyridine had been given. The patient's toxicity and his hallucinations gradually disappeared. His white blood cell count increased to 23,000 per cu.mm., exceeding 10,000 for the first time since his admission. There were 76 per cent polymorphonuclear neutrophils. A blood culture, taken immediately after the chill, revealed three colonies per cubic centimeter; six days later, there was one colony per cubic centimeter. X-ray examination of the chest four days after the chill still showed infiltrations in the right lower lobe, which were interpreted as indicating pneumonia or abscesses. One week later, the chest was clear. Meanwhile, the skin eruptions had subsided.

After 120,000 units of staphylococcus antitoxin had been administered, its use was discontinued. The number of transfusions was reduced to one weekly. Sulfapyridine was very well tolerated. The administration of this drug alone was continued, the dosage being 6 grams per day. At the end of the third week of the patient's stay in the hospital he developed pain in the left hip. Traction was applied and the pain subsided within ten days. X-ray examination of the pelvis at this time disclosed no definite pathology. In the meantime, two blood cultures had been reported as sterile. Five weeks after admission to the hospital, the patient's white blood cell count dropped to 4,000 per cu.mm., and the hemoglobin to 64 per cent. For this reason, discontinuation of the sulfapyridine appeared to be indicated. In all, 142 grams had been given.

During the next two weeks the patient's general condition gradually improved. Evening temperature rises, however, up to 101°F., persisted. A sequestrum had to be removed from the still draining clavicle wound. Seven weeks after the onset of his illness, the patient was allowed out of bed. At this time, a check-up X-ray examination of the chest was done and reported as normal, except for the incidental finding of a destructive lesion in the right humerus. X-ray examination of the long bones then disclosed osteomyelitic processes in the left tibia and both humeri with sequestrum formation in the latter. None of these foci had given rise to complaints and on close examination, a swelling of the right humerus was the only objective finding. Since the metastatic lesions in skin and lungs had subsided without interference, it was felt that surgical intervention for the bone lesions could be safely deferred.

Under supportive therapy, consisting of dietary measures, iron and vitamin medication, and blood transfusions, the patient's general condition continued to improve. The hemoglobin increased to 75 per cent. The patient gained weight, became stronger and was able to walk about. His temperature ceased to rise above 100°F. Another sequestrum from the clavicle was removed, following which drainage became minimal. After a stay of three months, the patient was discharged.

#### COMMENT

The mortality of *Staphylococcus aureus* septicemia is very high, figures varying from 70 to 90 per cent (1). The prognosis may depend on the

initial defense reaction of the body as demonstrated in the leucocyte count and percentage of the polymorphonuclear neutrophiles, on the number of colonies per cubic centimeter in the blood culture, and on the nature and location of the metastatic foci. According to these factors, the case here reported had a very grave prognosis; the initial response with a white cell count of only 7,800 per cu.mm., with 84 per cent polymorphonuclear neutrophiles, was poor; the number of staphylococcus colonies in the first blood culture, (70 per cubic centimeter) was high; and, finally, the presence of metastatic lesions in the skin, aside from foci in bones, joints and lungs, had to be considered a most serious complication (2). Fortunately, heart and kidneys had remained intact.

In recent reports of recoveries from *Staphylococcus aureus* septicemia, four types of therapy were generally employed: 1) immediate drainage of metastatic foci; 2) repeated blood transfusions; 3) staphylococcus antitoxin and toxoid; 4) chemotherapy: sulfanilamide, sulfapyridine. All four types were used in the reported case.

It can be safely stated that the drainage of the clavicular focus was of no influence on the course of the sepsis. The definite value of the transfusions, however, in maintaining and stimulating the patient's resistance cannot be doubted. More difficult is the evaluation of the part which antitoxin and sulfapyridine played in the patient's recovery. In recent years, several reliable reports of recovery from grave *Staphylococcus aureus* septicemia under treatment with staphylococcus antitoxin have appeared with a course similar to the one presented (3 and 4). Though previous experiences with staphylococcus antitoxin were not encouraging, it must be stressed that the improvement in this case began after the chill which had followed the intravenous medication of the antitoxin. Favorable results with sulfanilamide in the treatment of staphylococcus aureus infections have been obtained but the superiority of sulfapyridine, the more recent chemotherapeutic agent, has been demonstrated in animal experiments (5). Clinical cases have been reported in which, after prolonged unsuccessful treatment with sulfanilamide, dramatic cure followed the administration of sulfapyridine (6, 7, and 8). For confirmation of its efficiency in this case sulfapyridine was tested *in vitro* against the patient's strain of *Staphylococcus aureus*. A strongly bactericidal effect was encountered. The combination of staphylococcus antitoxin and sulfanilamide in the treatment of overwhelming staphylococcus sepsis has been highly recommended with striking results (9). The conclusion may be drawn that the combination of antitoxin and sulfapyridine is even more efficient, and, in this case, should be considered responsible for the successful result.

It must be emphasized that the therapeutic result in the reported case is to be regarded as a recovery, not as a cure, from a fulminating *Staphylococcus aureus* sepsis. The possibility is that, though metastatic lesions



had been observed to subside spontaneously, foci, still present, may break down, blood stream invasion may recur, and the picture of chronic staphylococcus sepsis may ensue.

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# THE TECHNIQUE OF HANDLING PROTAMINE ZINC INSULIN

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Like most biological products, insulin is comparatively perishable. Thus, certain precautions must be observed in handling this product.

Obviously it would be a grave situation were the diabetic not to receive the required insulin at the exact strength stated on the label of the container. If it were stronger, then he would suffer insulin reactions; if it were weaker, he would develop glycosuria. For the benefit and safety of the diabetic, the Central Insulin Committee at the University of Toronto constantly checks and controls the products of all pharmaceutical houses engaged in the preparation and distribution of insulin.

Insulin should be protected from changes, and particularly from extremes of temperature. The safest place for storing insulin is the bottom of a refrigerator; here the temperature remains fairly constant and the insulin will not freeze. The purchasing of insulin from a druggist who keeps the packages on the shelf, rather than in the refrigerator, should be avoided.

If the patient does not have a refrigerator in his home, he must make some other arrangement for storing the insulin where it will be protected from wide variations in temperature. The window-ledge cooler, used in northern climates as a substitute for a refrigerator, is not a safe storage place; here the variations in temperature are too great and too sudden. The insulin may freeze in winter and get too warm in summer. It must *never* be allowed to freeze, because its potency is thereby destroyed.

Protamine zinc insulin, being a suspension of tiny particles in a liquid, is particularly sensitive to heat and cold. If it is allowed to become too cold, these particles coalesce and come out of the suspension. When this happens the substance is useless. Unmodified insulin and zinc crystalline insulin are hardy and can stand wide variations in temperature but this does not invite careless handling.

All insulin, regardless of the source, is sold in various standard potencies. These strengths may be easily recognized by the legend and color of the label, as well as by the color of the container's rubber stopper. They are marked as follows:

Color of label	Insulin Units per cu. cm. of solution
Yellow	20
Red	40
Green	80
Black	100

Other specific strengths are available but are not generally sold.

These various potencies permit the patient to measure his dosage accurately and they also allow him to inject a minimum amount of fluid. For instance, an individual may require an injection of forty units strength. He may take 2 cc. of U 20 (20 units of insulin per cubic centimeter of fluid), or one cc. of U 40, or  $\frac{1}{2}$  cc. of U 80. Of course, the latter dose is the smallest amount of fluid and therefore the most comfortably tolerated. And a dose of  $\frac{1}{2}$  cc. is easily measured. If the patient must have a dose of 10 units he may take  $\frac{1}{2}$  cc. of U 20,  $\frac{1}{4}$  cc. of U 40, or  $\frac{1}{8}$  cc. of U 80. It is very difficult to measure a quantity as small as  $\frac{1}{8}$  cc. and avoid errors, whereas a  $\frac{1}{4}$  cc. dose may be measured accurately; therefore, this patient will use U 40 strength insulin. He could use U 20, but this potency is usually reserved for doses of 5 units or less. Where doses of from 10 to 20 units are required, U 40 is advised; for doses of 20 units or more, U 80 is indicated.

Unmodified and zinc crystalline insulins are water-clear, aqueous *solutions*; protamine zinc insulin is a turbid, milky-white *suspension* in an aqueous medium. Its active ingredients are not dissolved, but are contained in minute suspended particles, and hence it requires special handling so as to insure uniform distribution of these particles throughout the liquid before any of it is withdrawn from the container. Unless this is done the user cannot be certain that he will get successive doses of uniform strength from a given container.

The method of securing this uniform distribution is an important part of the technique of handling insulin. First of all, violent shaking of the insulin container should be avoided, since this causes the liquid to froth, thus drawing some of the particles out of suspension. The liquid should be agitated as follows: grasp the container at top and bottom, between thumb and fingers, then turn the hand slowly so that the liquid is sloshed from end to end of the bottle. Continue this motion about twenty times. This agitation must be the final operation immediately before injecting the insulin. Do not stir up the solution and then set the bottle aside while preparing the needle, alcohol, cotton, etc., for in doing so the active ingredients are permitted to settle out again.

The syringe used for injecting protamine zinc insulin should be sterilized, when in use, each day by boiling it in water for ten minutes, for the old technique of keeping the syringe in alcohol is not satisfactory, as the droplets of alcohol which may cling to the instrument have a very detrimental effect on protamine zinc insulin.

A simple method of sterilizing syringes is to procure a large, coarse kitchen sieve that will comfortably hold the syringe-barrel, plunger, and needle. Remove the plunger from the barrel and place these parts, along with two needles, into the sieve. (Stainless steel, 25-gauge needles,  $\frac{3}{4}$  inch length, are recommended.) Immerse the sieve in boiling water for ten minutes.

At the end of a *full* ten minutes, remove the sieve and allow the water to drain off. Pour the water from the vessel, then rest the sieve across its top; this hold the instruments away from any surface which might contaminate them. After having washed the hands thoroughly, grasp the barrel of the syringe in one hand, the head of the plunger in the other. Insert the plunger into the barrel, making certain that no part of the instrument which will come in contact with the insulin is touched by the hands. Next, shake the sieve slightly until the points of the needles drop through the mesh, and the hubs are held in an upright position. Now it is possible to insert the tip of the barrel into the hub of one needle without touching either part, thus avoiding contamination. Care must be exercised to make sure that the point of the needle is not bent or broken; otherwise the injection may be painful.

Move the plunger of the syringe in and out several times. This will expel any water that may have remained in the barrel, and it will also help to cool the instrument. Remember that the needle and syringe must be at room temperature when the insulin is withdrawn from the container; if it is too warm, the potency of the hormone may be affected. With the plunger completely depressed, put the assembled syringe and needle aside. The lid of the box in which the insulin vial is packed will serve as a cradle for the syringe at this time; when the box lid is laid on the table, top down, the two thumb-notches will hold the syringe very firmly. Many people cover the table on which they are working with a coarse towel that has been pressed with a very hot iron. The towel then serves as a semi-sterile background for the operation.

Having assembled the syringe and needle, place it aside. Place a bit of absorbent cotton, soaked in alcohol, where it can be reached conveniently. Now take the insulin vial, agitate it as described above, and place it on the table in an upright position. Next, wipe the stopper of the bottle with alcohol; this prevents the needle, when penetrating the rubber, from contacting any surface which might not be sterile.

Taking up the syringe again, withdraw the plunger and fill the barrel with an amount of air equivalent to the quantity of insulin to be injected. In other words, if 40 units of the liquid is desired, pull the plunger back to the 40 unit mark; naturally, the barrel now contains the equivalent amount of air. Next, press the tip of the needle through the rubber stopper into the vial until it has just penetrated, but has not entered, the fluid. Depress the plunger. Never allow the air to bubble through the fluid; to do so causes frothing.

The vial now has an internal air pressure which helps to withdraw the insulin quickly. (Each time a new vial of insulin is started, an extra syringeful of air should be injected in order to create a reserve internal pressure.) Quickly invert the vial with the needle and syringe in place, agitate the liquid slightly, and withdraw the plunger to that calibration



which gives the exact amount of insulin required. Usually a small air bubble appears in the syringe; this is forced back into the vial, and the plunger is once more withdrawn to the proper calibration before removing the needle from the bottle. (Some syringes have two calibrated scales, one for U 20 insulin and one for U 40. *Make certain when using a syringe of this type that the proper scale is being read.*)

There are two reasons for measuring the insulin accurately *before* withdrawing the needle from the rubber stopper. One is that of economy, for if too much insulin is taken from the vial, a few drops will have to be pressed out as waste. In the second place, the rubber acts as a wiper to remove any insulin from the outside of the needle; therefore, the plunger should not be touched after the needle is withdrawn. If a tiny droplet of protamine zinc insulin remains on the outside of the needle at the time of the injection, it may be deposited in the tissue just below the skin, causing local irritation, redness, and swelling.

The carefully filled syringe is now set aside while the area of skin selected for injection is washed with alcohol. This done, pinch up the skin with thumb and forefinger and stretch it taut. This needle is inserted with a quick thrust and *at right angles to the skin surface*, and the insulin is introduced by a slow, steady pressure on the plunger. The needle should always be inserted at least three-quarters of its length; and the plunger, just before pressing it, should be withdrawn a fraction of an inch to make certain that a blood vessel has not been punctured. This is important, because protamine zinc insulin has no effect when it is injected directly into the blood stream. When the complete dose of insulin is injected, the needle is withdrawn, and the skin-puncture is wiped with alcohol.

The usual sites of injection are the outer aspects of either thigh, of either arm, or the abdomen. As a matter of fact, the injection may be made at any place on the body where the skin is loose enough, and where bones are not too close to the surface.

If protamine zinc insulin is being used, it should be injected *at right angles to the skin surface*. This is to minimize the area of skin through which the needle travels. When the needle goes in at right angles, only the skin which immediately surrounds the puncture can be irritated; if, however, the needle travels obliquely, all the skin which lies along its path may react uncomfortably.

With the injection completed, the needle and syringe should be rinsed immediately, inside and out, for if this is not done the residual liquid will become sticky and interfere subsequently with the smooth operation of the plunger. Cold tap water is quite satisfactory for this rinsing.

The best alcohol for disinfecting the skin and the vial stopper is 70 per cent grain alcohol. Rubbing alcohol is also satisfactory, as long as the user is not allergic to denaturants it contains. Such allergy will cause annoying irritations of the skin.

## CLINICAL PATHOLOGICAL CONFERENCE

GEORGE BAEHR, M.D., AND PAUL KLEMPERER, M.D., *presiding*

*Wednesday, February 15, 1939*

Arteriolar Nephrosclerosis Superimposed on Antecedent Glomerulonephritis and Terminating with Clinical and Pathological Findings of "Malignant" Acceleration. Rôle of Heart Failure in the Final Picture

*(From the Medical Service of Dr. B. S. Oppenheimer)*

*History* (Adm. 417281; P.M. 10980). The patient, a 50 year old Russian grocer, was first admitted to the hospital on November 30, 1937 because of dyspnea of three weeks' duration. One year previously high blood pressure had been discovered. At that time he had been hospitalized at another institution (Bronx Hospital) for investigation of the cause of attacks of severe substernal pain which followed each meal. X-ray examinations of the gastro-intestinal tract revealed a 2 cm. niche on the lesser curvature of the stomach and, in addition, an irregular duodenal bulb. The heart was rather markedly hypertrophied and an electrocardiogram was interpreted as showing evidence of myocardial damage. He was treated by diet and remained free of digestive complaints. Three weeks before admission he was awakened suddenly from sleep by severe dyspnea. From that time on he had suffered dyspnea upon exertion. He was treated by his physician without relief and therefore sought hospitalization.

*Examination.* The patient was a very orthopneic and dyspneic man, who, in the course of the examination, went into frank pulmonary edema. Fundi showed slight blurring of the nerve heads, especially nasally, with striation of the retina. Several hemorrhages and exudates were seen. The arterioles were narrowed, irregular, and tortuous with moderate A-V compression. The neck veins were distended. The heart was enlarged; a systolic murmur was heard at the apex; A2 was greater than P2. The rhythm was regular. The lungs revealed dullness at the right base with moist râles throughout both lower halves of the lungs. The liver was palpable three finger-breadths below the costal margin. Blood pressure was 235 systolic and 150 diastolic.

*Laboratory Data.* Hemoglobin, 54 per cent; red blood count, 3,200,000; white blood count, 9,000 (polymorphonuclear neutrophils, 69 per cent). Urine showed a maximum concentration at 1.014 with a very faint trace to a trace of albumin and no sugar. Microscopic examination revealed occasional hyaline casts, white blood cells and a rare red blood cell. The stool was guaiac negative. Venous pressure was 7 centimeters, rising to 8 centimeters on right upper quadrant pressure. Saccharine time was 25 seconds. Blood urea nitrogen, 45 mg. per 100 c.c. Cholesterol,

375 mg. per 100 c.c. Electrocardiogram showed sinus arrhythmia with periods of sino-auricular block. There was a slurred QRS; T<sub>1</sub>, T<sub>2</sub> and T<sub>4</sub> diphasic; with RT depressed in leads I, II, and IV. Serial changes were interpreted at first as being very suggestive of recent myocardial infarction but later this was thought improbable. X-ray examination of the chest showed enlargement of the heart in all diameters, exaggeration of pulmonary markings indicative of congestion, and a moderate amount of fluid at both bases.

*Course.* The impression upon admission was essential hypertension, arteriosclerotic and hypertensive heart disease, and left ventricular failure. The patient was immediately phlebotomized with relief of the pulmonary edema. The blood pressure fell to 210 systolic and 100 diastolic and later to a more constant level of 175 systolic and 110 diastolic. The patient improved with bed rest, sedatives and iron therapy. The blood pressure remained elevated but at a lower level, 165 systolic and 100 diastolic. The hemoglobin rose to 72 per cent. An ophthalmological consultant expressed the view that, although blurring of the discs was seen, the fundus was not that of "malignant" hypertension. Despite this, the medical staff felt that this was a case of "malignant" hypertension. The patient was discharged, improved, on December 29, 1937 after four weeks in the hospital.

*Second Admission* (January 20 to January 30, 1938). One month after his first discharge the patient was readmitted because of a severe attack of dyspnea lasting three hours.

*Examination.* There was little change in his condition. Blood pressure was 240 systolic and 147 diastolic.

*Laboratory Data.* Hemoglobin, 65 per cent; red blood count, 3,800,000; white blood count, 9,900 (polymorphonuclear neutrophils, 57 per cent). Urine showed a maximum concentration at 1.012; there was a faint trace to a trace of albumin; microscopic examination was unchanged. Stool guaiac, four plus. Venous pressure was 5.5 cm. with a rise to 6.5 cm. Saccharine time was 22 seconds. Blood urea nitrogen was 38 mg. per 100 c.c. Electrocardiographic and X-ray examinations of the chest were unchanged. Treatment consisted of phlebotomy of 350 c.c. Morphine and atropine, tourniquets to all extremities, and oxygen, mercupurin, digitalis, and ammonium chloride were administered. Clinically, the patient improved. His blood pressure fell to 186 systolic and 130 diastolic. Urea nitrogen rose to 53 mg. He was discharged after twelve days.

*Third Admission* (March 13 to April 3, 1938). The patient was admitted in pulmonary edema six weeks after his second discharge.

*Examination.* His lungs were filled with moist râles. His blood pressure was 190 systolic and 110 diastolic.

*Laboratory Data.* Blood urea nitrogen was 52 mg.; CO<sub>2</sub> combining power, 35.8 vol. per cent. Urine concentrated again only to 1.012 and showed albumin and occasional red blood cells microscopically. A Rehfuess test meal at this time showed no free acid even after histamine.

*Course.* Treatment consisted of morphine and atropine, 200 c.c. of 50 per cent sucrose, a 300 c.c. phlebotomy, and oxygen. He improved and because his hemoglobin was 56 per cent, it was decided to give him back the blood which had been taken from him. This was done by slow intravenous drip without mishap. Hemoglobin rose to 75 per cent. An ophthalmological consultant proclaimed the nerve heads to be normal. The patient was digitalized in order to prevent the episodes of left ventricular failure. He was finally discharged three weeks after admission, at which time the blood pressure was 150 systolic and 90 diastolic. The diagnosis was malignant nephrosclerosis.

*Fourth Admission.* On November 12, 1938, seven and a half months after his third discharge, the patient was readmitted to the hospital. During the interim



the patient had begun to have attacks of precordial oppression which were relieved by nitroglycerine. Nocturia three to four times was present. Immediately before admission, dyspnea, orthopnea and chest oppression became unbearable. Further inquiry at this time revealed the following additional facts which had not been obtained previously. At the age of 25, without predisposing infection, the patient had an episode of "swelling" of the face and legs which lasted about six months. At that time a physician had put him upon a low protein diet. Urine examination showed evidence of renal involvement. The edema gradually subsided and he had had no recurrences.

*Examination.* The patient was in marked dyspnea and orthopnea. Fundi showed slight blurring of the nasal margins of both discs (confirmed by ophthalmologist). Other changes included new hemorrhages and exudates.

*Laboratory Data.* Blood pressure 215 systolic and 125 diastolic. Hemoglobin, 53 per cent; red blood count, 2,800,000; white blood count, 6,800 (polymorphonuclear neutrophils, 73 per cent). Urine showed a maximum concentration at 1.012. Albumin, 1 plus to 2 plus. Microscopic examination showed 20 to 30 white blood cells and an occasional red blood cell. Venous pressure was 8.5 cm. with a rise to 12.5 cm. Saccharine time, 27 seconds; sedimentation time, 10 minutes; blood urea nitrogen, 74 mg. per 100 c.c.; cholesterol, 340 mg.

*Course.* Because of the new facts in the past history suggestive of an acute glomerulonephritis and the continuous renal impairment, as shown by fixed specific gravity and azotemia, a diagnosis of chronic glomerulonephritis was made. The course was progressively downhill with increasing evidence of cardiac failure and finally culminated in death one week after the last admission and one year after the first admission.

*Necropsy Findings.* The heart was tremendously enlarged, weighing 630 grams. Both the right and left ventricles were hypertrophied, as well as dilated. Throughout the myocardium, there were areas of marked fibrosis. These were secondary to the severe grades of sclerosis and narrowing of the coronary arteries. No actual occlusion of the vessels was present. Both kidneys were smaller than normal, having a combined weight of 200 grams. They were similar in size, shape, and pathological findings. The surface was finely granular, the granules being yellow-red and the intervening areas blue-red. The color of the kidney as a whole was red. The cortex was very narrow. Microscopically there were definite changes in the glomeruli and the renal vessels. The glomeruli presented three types of changes: 1) many were completely fibrotic, leaving no clue as to the pathogenesis of the fibrosis; 2) many showed a considerable degree of cellular infiltration, as is found in inflammatory renal conditions; 3) other glomeruli showed areas of necrosis, as is characteristically found in the "vascular" kidney. The renal vessels showed marked arteriosclerosis with reduplication of the elastica. Some of the vessels, however, showed extreme narrowing of the lumen with a very cellular intima.

*Comment.* Dr. Klemperer. The renal findings indicate the presence of two different factors. On the one hand, the fine, regular surface granulations and the cellular glomerular infiltrations are indicative of chronic diffuse glomerulonephritis; on the other hand, the red color of the kidney, the occasional necrotic loops in some glomeruli, and the presence in some arteries of markedly narrowed lumina with very cellular intima are evidences of a vascular contracted kidney, a result of an acceleration of the usual tempo of arteriosclerosis that frequently accompanies chronic nephritis.



*Dr. Baehr.* The common conception that "malignant sclerosis" is always the end-stage of a primary hypertensive vascular disease is incorrect. On the contrary, it may be the end-result of any disease of the kidney which is associated with hypertension, such as chronic glomerulonephritis, bilateral congenital polycystic disease of the kidneys, hydro- or pyelonephritic contracted kidneys, and even amyloid contracted kidneys. The importance of this observation lies in the fact that it corrects the current impression that "malignant sclerosis" is a disease *sui generis*.

The case in hand exemplifies this fact. This patient had acute glomerulonephritis at the age of twenty-five. Then, following a long latent interval without any symptoms whatsoever, he developed severe arterial hypertension, and eventually also fundal changes characteristic of so-called "malignant sclerosis" and repeated attacks of heart failure. So typical were the findings that until his last admission, at which time the history of a previous nephritis was elicited, the clinical diagnosis was merely malignant nephrosclerosis. It was then recognized that this condition had been engrafted as a terminal event upon a hypertensive vascular disease due to chronic glomerulonephritis. The great frequency of this superimposition of the accelerated phase of arteriosclerosis upon chronic nephritis is clearly indicated by the analysis of the last fifty-five cases of nephritis autopsied at The Mount Sinai Hospital. All cases showed arteriosclerosis (36.4 per cent—slow, progressive arteriosclerosis; 45.4 per cent—accelerated arteriosclerosis (malignant sclerosis); 18.2 per cent—transitional stage). In other words, almost one-half of the cases of chronic glomerulonephritis had developed terminally a superimposed accelerated phase of arteriosclerosis, so-called malignant sclerosis.

Vascular Sequelae of Chronic Amyloid Disease Associated with Chronic Osteomyelitis and Resulting in Amyloid Contracted Kidneys and Secondary Hypertensive Vascular Disease; Terminal Clinical and Pathological Findings of So-called "Malignant" Acceleration.

(From the Medical Service of Dr. B. S. Oppenheimer)

*History* (Adm. 433942; P.M. 11028). *First admission* (May 17 to June 11, 1932). The patient was a twenty-four year old single male who had been well until 1926 when, at the age of 12, he was operated on for osteomyelitis of the spine at another institution (New York Orthopedic) where two spine fusions were done (D5 to D9 and L1 to S2), as well as drainage of a focus in the right femur. Following these operations he continued to have draining sinuses at the sites of operation. Staphylococcus aureus was cultured. In 1932, when 18 years old, a third operation was done at that institution and two large retroperitoneal abscesses were drained. A sinus, however, continued to discharge pus. While at the hospital following the last operation, he developed enlargement of the liver

and spleen and an albuminuria followed subsequently by edema of the lower extremities and ascites. After seven months he was discharged from that institution. Four months later (1932) he appeared for admission to The Mount Sinai Hospital because of fever and edema of the legs. One week previous to admission he had noticed bright red blood in his urine.

*Examination.* The patient was a chronically ill young man with general anasarea and marked enlargement of the abdomen. The fundi were negative. The lungs showed flatness at both bases. The heart was not enlarged. Blood pressure was 112 systolic and 70 diastolic. The abdomen showed dilatation of the superficial veins. The liver and spleen were markedly enlarged. The liver edge was palpable five finger-breaths below the costal margin; the spleen, at five finger-breadths below the costal margin. Shifting dullness and a fluid wave were present. The extremities showed moderate pitting edema. There were operative scars on the spine.

*Laboratory Data.* Hemoglobin, 43 per cent; red blood count, 3,200,000; white blood count, 12,320 (polymorphonuclear neutrophils, 90 per cent). There were 360,000 platelets. Urine showed a maximum concentration specific gravity of 1.016; there was a trace to plus albumin; sugar, 0; guaiac, 0 to two plus; microscopic, occasional red blood cell, white blood cells and casts. Stool, brown liquid guaiac 0 to four plus. Urea nitrogen, 8 mg. per 100 c.c. Total protein, 5.7 per cent; CO<sub>2</sub> combining power, 54.5 vol. per cent; albumin, 2.5; globulin, 3.2; cholesterol, 95 mg. per 100 c.c., repeated; calcium, 8.5; phosphorus, 3.5; chloride, 608. Blood Wassermann reaction was negative. Von Pirquet test was negative. Congo-red test showed 100 per cent retention of the dye. The right pleural space was aspirated and 150 c.c. of turbid fluid was obtained, with a cell count of 3,200 and total protein of 2.9 per cent. Guinea pig inoculations were negative. The ascites was tapped and 3500 c.c. of straw-colored fluid obtained. Specific gravity was 1.012; cell count, 560 cells (lymphocytes, 67 per cent); total protein, 2.4 per cent; guinea pig inoculation, negative; Lowenstein culture, negative. Tumor cells were not found. X-ray examinations of the spine showed the operative fusions. A barium enema showed no organic disease. The liver and spleen appeared enlarged.

*Course.* The clinical impression was amyloidosis; hepatosplenomegaly; amyloid nephrosis; ascites; bilateral hydrothorax; chronic osteomyelitis; tuberculosis (?).

The patient ran a febrile course during the three weeks in the hospital. He was started on liver extract therapy and finally discharged to a chronic disease hospital for continuance of this treatment. He was discharged from that institution after two months and continued to receive liver extract in our Out-Patient Department over a period of eighteen months. The hemoglobin rose progressively to 93 per cent. Edema disappeared. Liver and spleen remained palpable. He showed remarkable clinical improvement.

*Second Admission* (January 10 to January 18, 1934). He re-entered the hospital for incision and drainage of an abscess of the right thigh at the site of the previous drainage of an osteomyelitic focus in the right femur. X-ray examination showed no bone destruction. Pus was evacuated and upon culture *Staphylococcus aureus* was found. The blood urea nitrogen was 20 mg. per 100 c.c. The urine showed a very faint trace of albumin; specific gravity, up to 1.030; sugar, negative; microscopically there was an occasional granular cast. He was discharged at the end of one week, entirely afebrile. Following discharge he continued to do well. During this period liver extract was not administered. The liver was barely palpable; the spleen could be felt two finger-breadths below the costal margin. Albuminuria persisted. He continued to feel very well, went to work, gained weight and had no complaints.

After a lapse of three years, during which the patient felt fine and worked, he returned to the Follow-Up Clinic for routine check-up. At that time (February 21, 1938) his blood pressure was found to be 240 systolic and 146 diastolic. The blood urea nitrogen was 22 mg. per 100 c.c. Electrocardiogram showed no abnormality. X-ray examination of the chest showed an enlargement of the left ventricle. Urine contained 4 plus albumin. Congo-red test still showed 100 per cent retention of the dye.

*Third Admission* (December 4 to December 25, 1938). Six weeks before re-admission, he became unusually drowsy. Three days before admission he fell unconscious and frothed at the mouth. Unconsciousness lasted for three hours. Temperature rose to 102°F. From that time on until admission he had passed very little urine, was very restless, and complained of blurred vision. He had vomited once.

*Examination.* The patient was stuporous and had facial edema. The fundi revealed marked bilateral papilledema with numerous flame-shaped hemorrhages, exudates and star maculae; the arteries were extremely narrowed. The lungs showed a friction rub at the right axilla. The heart was enlarged; a systolic murmur and gallop rhythm were present. Blood pressure was 210 systolic and 140 diastolic. The liver edge was palpable three finger-breadths below the costal margin. There were ecchymoses and slight pitting edema over both tibiae. A positive Trousseau sign was elicited and a left Babinski sign was present.

*Laboratory Data.* Hemoglobin was 64 per cent. The urine had a specific gravity of 1.012 with 3 plus albumin and innumerable red blood cells. The impression was amyloid contracted kidneys and uremia.

*Course.* The patient remained in coma. Intravenous sucrose and calcium gluconate, as well as Hartman's solution, were administered. The patient, however, did not respond and died within twenty-four hours.

*Necropsy Findings.* The third and fourth lumbar vertebrae of the *spinal column* were fused; the intervertebral disc was completely absent. The prevertebral fascia was thickened, fibrotic and cicatricial. This tissue formed a large retroperitoneal plaque-like mass, densely adherent to the lumbar vertebrae. Both *ureters* were caught within this mass and were partially stenosed. The *kidney, liver and spleen* showed involvement by amyloidosis. The spleen presented the diffuse, rather than the sago, type of amyloid involvement. The liver surface showed distinct granularity, suggestive of an "amyloid contracted" liver. This is seen very rarely and only in severe cases. The kidneys were atrophic. The color was distinctly yellow as a result of fatty infiltration. They were waxy in appearance and very firm to the touch. There was bilateral hydronephrosis, left more marked than right, in consequence of the partial bilateral ureteral stenosis. The glomeruli appeared large and anemic, while microscopically they were universally involved by the amyloidosis with resulting marked interference with the circulation. The renal contraction was chiefly a result of the amyloidosis, with the hydronephrosis acting only as a contributory factor. The *heart* was enlarged, involving chiefly the left ventricle. The *intestine* revealed uremic ulceration.

Microscopically, the vessels of the kidney chiefly, but also those of other organs, e.g., the pancreas, showed extremely narrowed lumina. Some showed many large foam cells in the intima, so frequently seen in the accelerated phase of arteriosclerosis, while others showed unquestionable arteriolonecrosis. These features of the vascular lesions are characteristic of the accelerated form of arteriosclerosis.

*Comment.* Dr. Baehr: So-called "malignant hypertension" can, and does, occur as the end stage of any renal disease associated with hypertension, regardless of the underlying cause of the renal damage. So-called

malignant sclerosis is merely the unmistakable evidence of an accelerated tempo of the arteriosclerotic process which developed regularly as a secondary phenomenon in renal disease with hypertension, whether the primary renal damage be acute glomerulonephritis, hydro- or pyelonephritis, congenital polycystic disease or amyloid disease of the kidneys. This case, for example, showed marked hypertension and fundal changes and cerebral symptoms typical of "malignant hypertension". Yet the underlying pathology was amyloid contracted kidneys with a superimposed renal and systemic accelerated phase of arteriosclerosis. Such vascular changes may develop in any form of hypertension.

In connection with the use of liver extract in an attempt to induce regression of amyloidosis, I wish to refer to the experimental work of Grayzel, Jacobi, et al. Although liver extract was successful in early cases, once the process had become moderately advanced or well advanced, there was no longer any beneficial effect. In this case there did appear to be definite, even if only temporary, benefit. However, the rise of hemoglobin from 40 to 93 per cent, as well as a disappearance of the suppuration, might have been sufficient to account for any apparent improvement without necessarily invoking any direct effect on the amyloid deposits.

Reported by *Max Ellenberg, M.D.*



## CLINICAL NEUROPATHOLOGICAL CONFERENCE

*Monday, February 13, 1939*

JOSEPH H. GLOBUS, M.D., *presiding*

*Case 7.<sup>1</sup> Multiple Sclerosis*

*(From the Neurological Service of Dr. I. S. Wechsler and the Neurosurgical Service of Dr. I. Cohen)*

*History* (Adm. 403605; P. M. 10236). A laborer, aged 56 years, who had been employed as a brass worker for thirty years, was admitted to the hospital on January 18, 1937 complaining of progressively increasing weakness of the legs. At the age of 32 he had had an operation for a traumatic cataract in the left eye. Four years before admission (1933) he fell a distance of five feet and struck the left side of his head. He was unconscious for a period of fifteen minutes. Since this accident he had experienced episodes of headache and vertigo with a tendency to fall to the left. He developed a coarse tremor of the head and frequently had difficulty in finding words with which to express himself, often employing them in faulty sequence, or using the wrong words. There appeared a definite change in his personality; his memory became poor, he was no longer capable of a sustained mental effort, he became irritable and easily excitable and was often heard muttering to himself. One year after the fall, and following a tonsillectomy, the tremor of his head disappeared (to return in a more marked degree two and one-half years later). For one and a half years following the fall he experienced a continuous whistling noise in the left ear; this also disappeared for a while but returned later in transient episodes. At the same time progressive loss of hearing in that ear became apparent. During the two years before admission weakness of the left leg developed, and he occasionally would fall to the left side. His handwriting during the same time had become rather wavy.

*Examination.* The patient was well-developed but poorly nourished. There was a marked bilateral arcus senilis. In the left eye there was evidence of a previous iridectomy. There were hypertrophic changes in the finger joints. His chest was emphysematous in type; the heart sounds were faint; the blood pressure was 120 systolic and 75 diastolic; and there was peripheral sclerosis.

*Neurological Status.* The patient held his head tilted to the left. There was a nodding tremor of the head which would disappear when the head was supported.

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<sup>1</sup> The first six cases presented at this conference appeared in the preceding two issues of the Journal (Volume 6, numbers 4 and 5.)

His gait was markedly ataxic. The Romberg sign was present. The right fundal vessels showed arteriosclerotic changes. There was paralysis of the left internal rectus muscle and paresis of the right internal rectus muscle. There was horizontal and vertical nystagmus. A slight left facial weakness was present. A moderate degree of nerve deafness was found in the left ear. Caloric and hearing tests indicated a central lesion without definite localization. The reflexes on the right side were more active than those on the left. All the abdominal reflexes and the right cremasteric were absent. There was a bilateral Babinski sign, more marked on the left side. Generalized atrophy and flabbiness of the musculature, moderate hyper-tonus in the upper extremities, and marked spasticity of the lower extremities, more marked on the right side, were noted. The heel-to-knee test was performed poorly and there was slight impairment of position sense in the toes.

*Laboratory Data.* The cerebrospinal fluid was under normal pressure. It contained one cell (monocyte) per cubic millimeter. The Pandy test was 4 plus; the total protein, 82 mg. per cent. Hemoglobin, 110 per cent; red blood cells, 4,880,000; color index, 1.1. Blood and cerebrospinal fluid serology were negative. The twenty-four hour urine was positive for lead and showed one plus albumin. The electrocardiogram showed changes indicative of myocardial damage.

*Course.* A diffuse process affecting the pyramidal tracts, basal ganglia, cerebellar pathways, and cranial nerves was thought to be responsible for the clinical manifestations. It was felt, however, that the patient's age tended to exclude multiple sclerosis as a diagnostic probability. Olivo-cerebello-pontine atrophy was ruled out by the predominance of pyramidal tract signs. Chronic encephalitis was also considered. A cerebral neoplasm could not, however, be fully ruled out and encephalography was suggested. The encephalogram revealed a symmetrical dilatation of the lateral ventricles and of the third ventricle. The fourth ventricle could not be visualized. In the course of the air injection the patient's pulse and respirations stopped—they returned on the administration of stimulants. A suboccipital craniotomy was then performed. No tumor was found. Four days after operation the patient developed bronchopneumonia and died.

*Necropsy Findings. Brain. Gross.* A considerable amount of yellowish fluid filled the subarachnoid space. The gyri of the cortex were narrowed and the sulci were widened. The brain substance was of firm consistency.

On sectioning the brain, the ventricular system showed a symmetrical dilatation anterior to the aqueduct. The aqueduct itself was rounded but not enlarged. The fourth ventricle was somewhat larger than normal. Small areas were seen in the left parietal subcortex resembling sclerotic plaques. A coronal section at the level of the head of the caudate nucleus showed clear-cut areas of sclerosis in the subcortex (fig. 19). The dentate nuclei were smaller in size than normal and were not well-outlined. The inferior olives also appeared smaller than normal and poorly demarcated.

*Microscopic.* Sections, obtained from the cerebral hemispheres and brain stem and stained for myelin, showed many sharply defined areas of demyelination. In the medulla oblongata at the lower level of the pyramidal decussation there was one large area involving the funiculus cuneatus, Lissauer's tract, the descending root of the trigeminal nerve and its nucleus, and the dorsal spinal cerebellar tract. In addition there were several smaller scattered plaques. In a section through the pons and cerebellum there were scattered areas of demyelination in the brachium pontis, one large area in the lateral part of the tegmentum extending into the brachium pontis, and several other plaques (fig. 20A); fiber tracts bordering on the periventricular gray substance were also affected. The sharp transition between the myelinated area of a plaque and the adjacent intact tissue persisted even under higher magnification (fig. 20B). The products of the demyelination showed

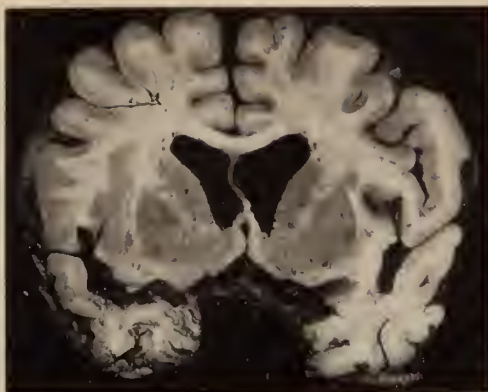


FIG. 19 (Case 7). A coronal section of the brain showing a large sclerotic patch in the white matter lateral to the left corpus striatum and scattered smaller patches elsewhere in the subcortex. The lateral ventricles are dilated.

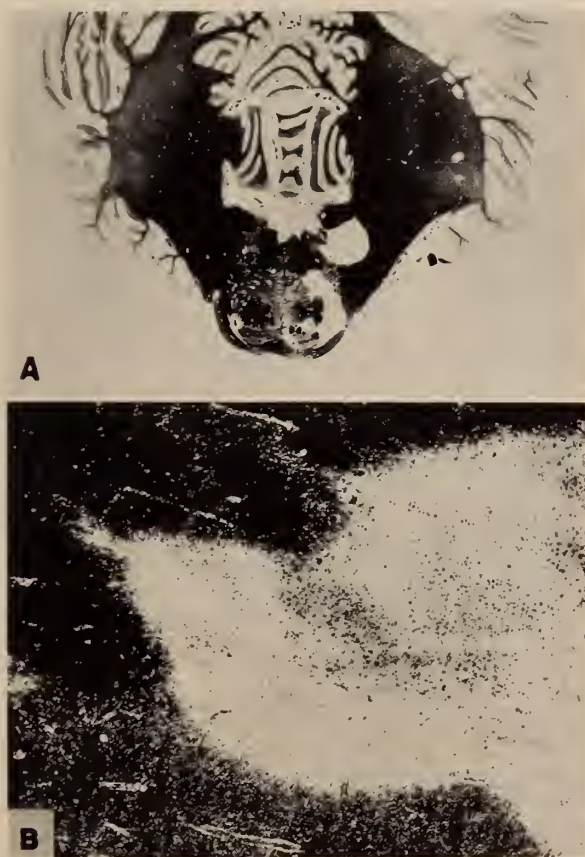


FIG. 20 (Case 7). A. Section of the pons showing multiple areas of demyelination in the tegmentum and brachium pontis (Weil stain).

B. Section of cerebral subcortex showing the fairly sharp delineation of a sclerotic plaque (Spielmeyer, microphotograph, 90 X).



a similar strict delimitation. The plaques were crowded with fat-laden, compound granular cells as shown in a preparation stained with Scarlet Red (fig. 21 A & B). Fat droplets were also present outside of cells. Blood vessels within the plaque were patent. The Globus modification of the Cajal gold sublimate stain disclosed swollen glia cells within the plaque contrasting with the smaller glia cells in adjacent, more normal brain tissue (fig. 22A). A Bielschowsky stain disclosed a large number of

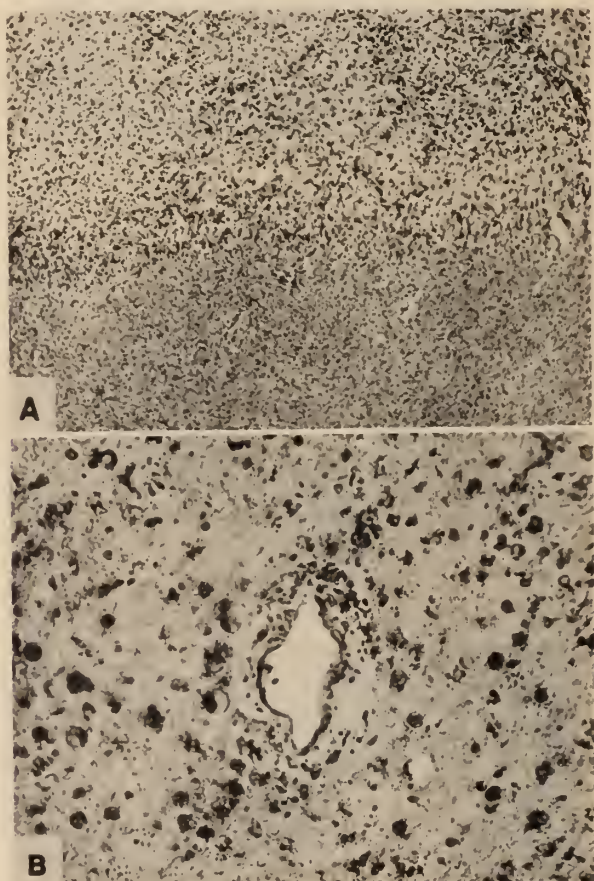


FIG. 21 (Case 7). A. An area of demyelination sharply delimited and crowded with fat-containing macrophages (Scarlet Red, microphotograph, 90  $\times$ ).

B. An area of demyelination under higher magnification showing a patent vessel and numerous fat-containing macrophages (compound granular cells) (Scarlet Red, microphotograph, 240  $\times$ ).

intact axis cylinders within the plaque. Desquamation of ependymal cells with subependymal glial fibrosis was seen in some parts of the wall of the lateral ventricle (fig. 22B).

*Comment* (Dr. Globus). The exception to the typical clinical entity is frequently a stumbling block to a correct diagnosis. In this instance,



were it not for the development of the neurological manifestations at the age of 52, the diagnosis of multiple sclerosis would have been accepted without much discussion. The disseminated character of the lesion, the recessions of a few symptoms, the nevertheless generally progressive character, and finally the manifestations of marked cerebellar involvement were all signs and symptoms favoring such a diagnosis. Neoplasm would hardly have been considered were it not for the age of the patient.

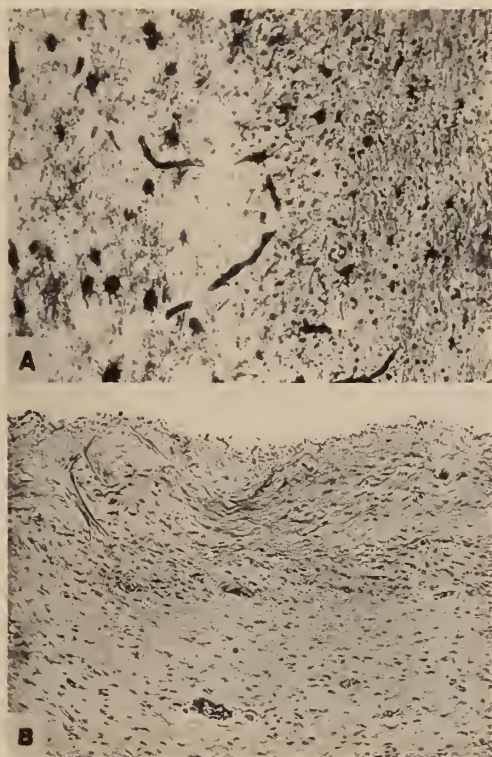


FIG. 22 (Case 7). *A.* A sclerotic plaque displaying swollen glia, which contrast strikingly with the smaller glia in the adjacent, relatively normal subcortex (Cajal gold sublimate, Globus modification, microphotograph, 215  $\times$ ).

*B.* Section of ventricular wall showing desquamated ependyma and a marked glial fibrosis in the subependyma (Hematoxylin-eosin, microphotograph, 90  $\times$ ).

The histopathological findings are typical of disseminated sclerosis. Of significance is the fact that the vessels in well-developed lesions are patent, an observation which is in conflict with the recently expressed view (Putnam) that the lesions in multiple sclerosis are the result of embolic phenomena. No less striking is the complete absence of inflammatory reactions, which excludes in this instance the relationship of multiple sclerosis to meningo-encephalo-myelitis.

Reported by *J. H. Friedman, M.D.*

## ABSTRACTS

AUTHOR'S ABSTRACTS OF PAPERS PUBLISHED ELSEWHERE BY MEMBERS OF THE  
MOUNT SINAI HOSPITAL STAFF

Members of the hospital staff and the out-patient department of The Mount Sinai Hospital are invited to submit for publication in this column brief abstracts of their articles appearing in other journals.

*Neural Correlations of Vision and Their Significance for Localization of Tumors of the Brain: A Preliminary Report.* CHARLES A. ELSBERG AND H. SPOTNITZ. Arch. Neurol. & Psychiat. 39: 315, February 1938.

In this paper the authors discuss the nature of dark adaptation of vision and the cerebral factors. They describe the results of tests in patients with tumors of the brain and conclude that functional visual tests have definite value for the localization of supratentorial neoplasms.

*A Theory of Retino-Cerebral Function with Formulas for Threshold Vision and Light and Dark Adaptation at the Fovea.* CHARLES A. ELSBERG AND H. SPOTNITZ. Am. J. Physiol. 121: 454, February 1938.

Based on tests of threshold vision and of light and dark adaptation, the authors have suggested formulas which are mathematical expressions of retino-cerebral functions. As the tests of dark adaptation have to do with conscious vision, the formulas apply to the conscious visual process.

*Does an Attack of Acute Anterior Poliomyelitis Confer Adequate Immunity? Report of four second attacks in New York City in 1935.* A. E. FISCHER AND M. STILLERMAN. J. A. M. A. 110: 569, February 19, 1938.

Four patients who had second attacks of poliomyelitis were seen during the New York City outbreak in 1935. The first attacks had occurred in 1930, 1931, or 1933. The literature was reviewed and a number of instances of authentic second attacks was found. The sera of one patient who was observed at the onset of his second attack was studied for neutralizing (protective) antibodies, the first patient with a second attack to be thus investigated. No antibodies were found in the serum of this patient three days, twenty-one days, and one year following the second attack. The number of second attacks in New York City in 1935 was large enough so that one must question the degree or permanency of immunity that develops from an initial infection with poliomyelitis virus. Inasmuch as a number of strains of this agent have been isolated in different epidemics and localities it is possible that the explanation for the second attack may lie in the fact that immunity to one strain of poliomyelitis virus does not necessarily confer immunity against other strains.

*The Surgical Treatment of Carcinoma of the Thoracic Esophagus.* With a Report of Three Successful Cases. J. H. GARLOCK. Surg. Gynec. & Obst. 66: 534, February 15, 1938.

The author calls attention to the fact that surgery of esophageal carcinoma has not kept pace with the rapid advance made in thoracic surgery. He stresses the ineffectual results obtained by x-ray therapy, and quotes statistics to prove that life expectancy with this treatment is not materially prolonged. A plea is made for early diagnosis before considerable weight loss has occurred. This will increase the percentage of operable cases and decrease the mortality rate. A detailed discussion of methods of diagnosis is given, including x-ray examination with the various mixtures of barium, esophagoscopy, biopsy of the tumor, etc. Thorough, careful ante-operative preparation is most important. The details of the operative technique are described with the aid of diagrams. Finally, the author reports in detail three cases that were subjected to the radical operation. There was no operative mortality.

*Gliomeuroma and Spongioneuroblastoma, Forms of Primary Neuroectodermal Tumors of the Brain.* J. H. GLOBUS. Am. J. Cancer 32: 163, February 1938.

The author calls attention to the fact that a tumor form, variously called neuroglioma, neuroglioma ganglionare, gangliogliomeuroma amyelicum, gangliogliomeuroma, ganglio glioma, etc., which hitherto was considered rare (only 29 cases being reported in the literature up to the time of publication), in reality occurs more frequently. He found a total of 22 cases (about 12 per cent) belonging to this group in a series of 178 proved supratentorial gliogenous tumors. The apparent rarity of this tumor form is attributed to the failure to use the Nissl staining method.

In view of the common derivation of nerve cells and neuroglial elements, the author points out that both types of cells may be expected to occur in tumors arising from the neuroectodermal tissue. He states that the actual frequent occurrence of such mixed glial and neuronie tumor types lends additional weight to the Cohnheim embryonal rest theory of tumor formation. Furthermore the occurrence of lesions in other parts of the brain in the spongioneuroblastoma relates this form to tuberous sclerosis, a blastomatous malformation of the nervous system, in which both types of cells participate.

The author subdivides this group of tumors into the gliomeuroma and spongioneuroblastoma, the former containing more mature glial and neuronie elements, the latter showing a more primitive, less well differentiated type of cell. He presents evidence favoring this division from the anatomical, histological and clinical points of view.

The *gliomeuromas* are distinguished grossly by their rubbery consistency, by their gradual merging into the surrounding normal brain tissue, and by their glistening, slimy, myxomatous appearance and firmness to the touch. Histologically there is a remarkable uniformity in their cellular content and arrangement. One finds a large number of fairly well differentiated nerve cells distributed among a fairly dense mass of equally well differentiated neuroglial elements. Both types bear a strong resemblance to cells in the young brain. Undifferentiated elements and giant or malformed cells occur rarely.

Clinically the gliomeuromas are characterized by the precipitate onset of symptoms, with either a Jacksonian convulsion, recurrent petit mal attacks or transient loss of consciousness ushering in the illness. It progresses rapidly, with the convulsive seizures occurring more frequently, with the development of intellectual depreciation and focal signs, and terminates after an abrupt accentuation of the signs and symptoms, in death.

The *spongioneuroblastomas* represent, as mentioned above, a more primitive stage of development than the gliomeuroma. Grossly they almost invariably lie deep in

the hemisphere, near the strio-thalamic angle. They have a friable granular surface and can be distinguished fairly readily from the adjacent normal brain tissue. Histologically one finds nest-like aggregations of neuroblasts and spongioblasts, the latter resembling the glial elements found in the spongioblastoma multiforme. In addition, in other parts of the brain there are lesions with malformed and giant neuronc elements, which resemble either fully developed or abortive forms of tuberous sclerosis. Clinically they resemble the glioneuroma with regard to the onset of the symptoms, but the uninterrupted and rapid progression of the clinical signs and symptoms serves to distinguish them from the majority of the glioneuroma group.

The most important conclusions which the author reaches are that the two tumor types described represent distinct entities in which both glioblastic and neuroblastic elements are present, and that the "proper evaluation of the histological character of these tumors gives promise of clarifying the understanding of the genesis of primary brain tumors," particularly in the light of the Cohnheim embryonal rest theory of tumor formation.

E. P. Mindlin

*Studies of Gaucher Cells by Supravital Technique.* L. A. ERF. Am. J. M. Sc. 195: 144, February 1938.

Gaucher cells were studied by means of the supravital method of Sabin. The material was obtained by means of sternal puncture or from scrapings of Gaucher spleens immediately after operation. The cells varied in size according to their age. As the cells became older, the mitochondria disappeared while the keratin fibrils increased in numbers in the cytoplasm. In the older cells an unknown alcohol-soluble substance accumulated in the cell cytoplasm as refractile granules. In sections and stains, these granules were removed by alcohol and the cells appeared vacuolated. Vacuoles were very rarely found in the cells by supravital examination and no phagocytosis was observed. That Gaucher cells are not motile but that the cytoplasm of the younger cells is fluid was evidenced by the fact that the fibrils and mitochondria could and did move in the cytoplasm.

The origin and function of Gaucher cells could not be determined by this supravital study.

*Segmental Enteritis.* RICHARD LEWISOHN. Surg. Gynec. & Obst. 66: 215, February 1938.

Segmental or regional enteritis is not a rare disease. Opinions differ widely not only as to the pathogenesis of these interesting lesions, but also as to the best method of surgical treatment. This lesion is encountered most frequently in the terminal ileum. However, it may occur in any part of the gastro-intestinal tract. It is doubtful whether segmental ileitis and ileocolitis are clinical entities. They may represent an attenuated form of acute ulcerative colitis and ileitis. Perianal fistulas are frequently encountered. Ileocolostomy with division of the ileum may effect a complete cure. In the presence of fistulous communications with other parts of the intestinal tract primary resection becomes mandatory.



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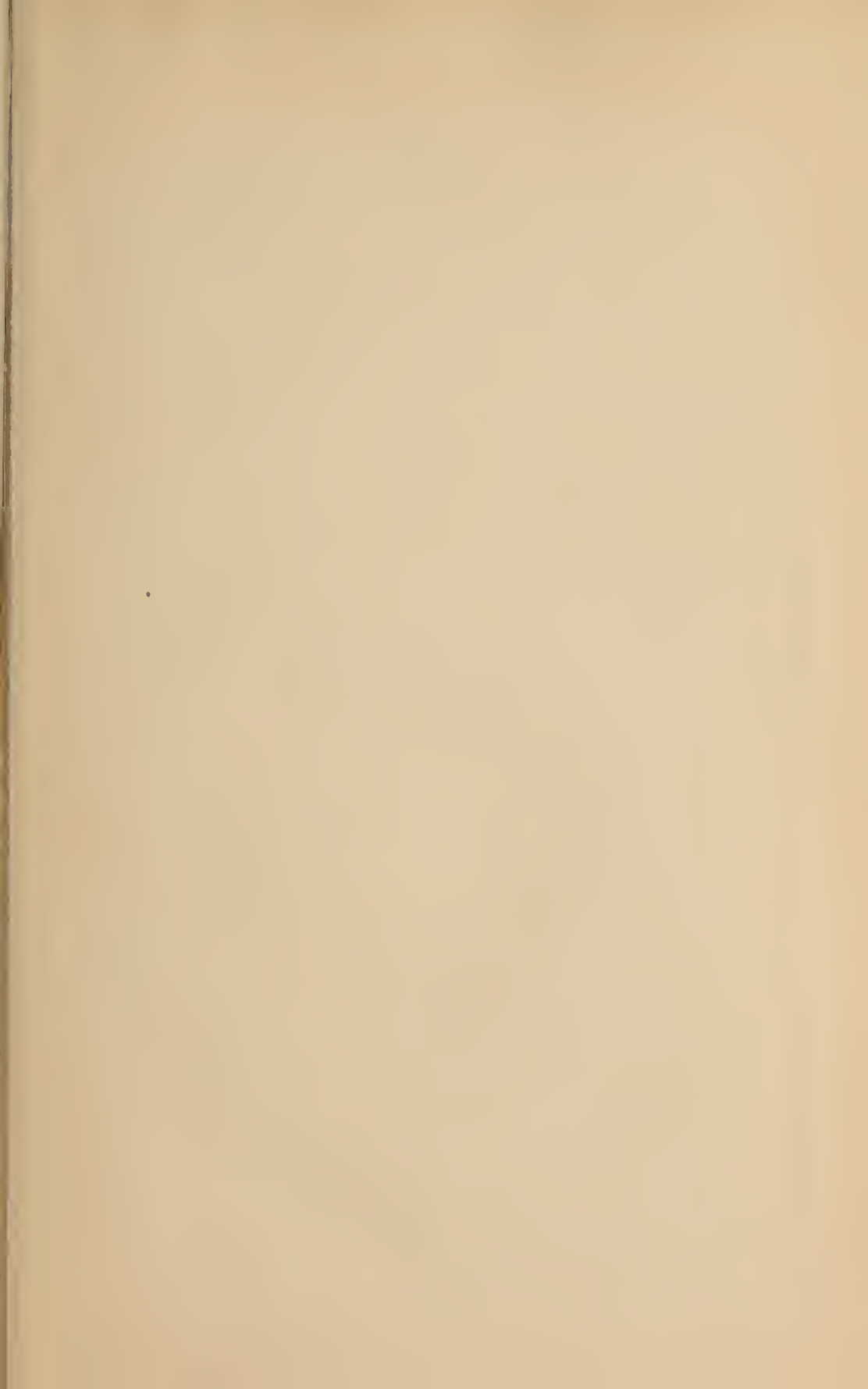


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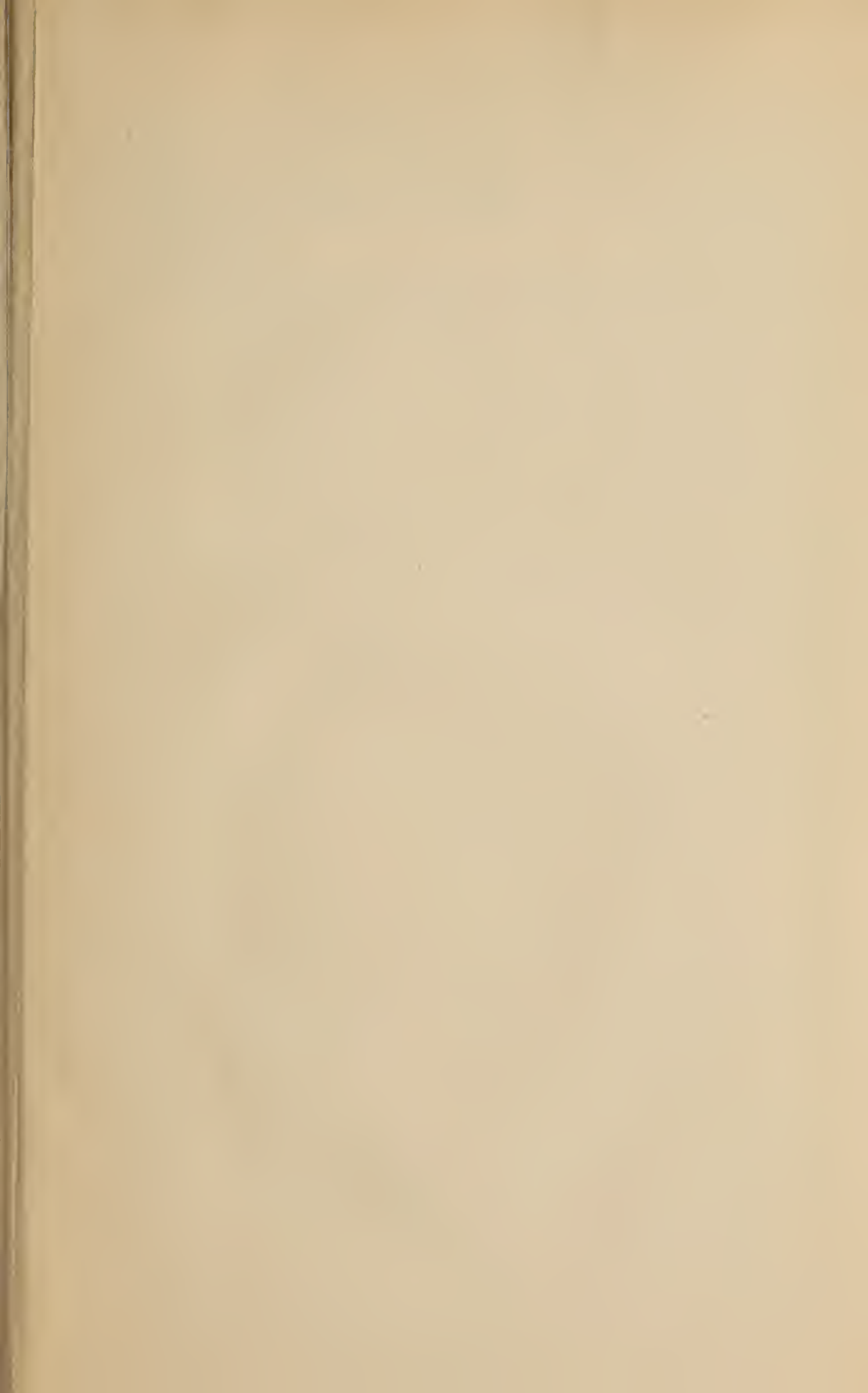
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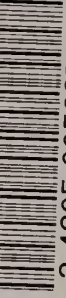


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